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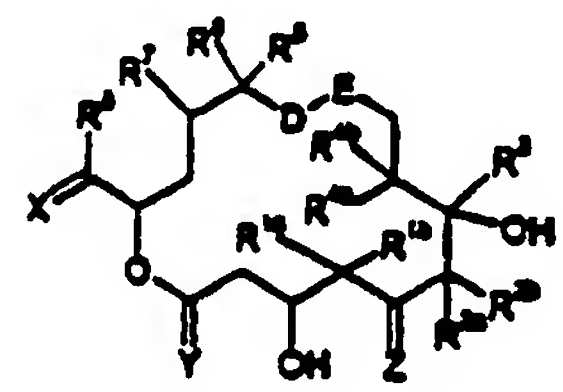

(I)

57) Abstract

The invention relates to new epothilone derivatives of the general formula (I), in which the substituents Y, Z, R^{1a}, R^{2b}, R^{4a}, R^{4b}, D–E, R^5, R^6, R^7, R^8 and X have the meanings assigned to them in the description. The new compounds interact with tubulin by stabilizing formed microtubuli. They are capable of influencing cell division in a phase-specific manner and are suitable for the treatment of malignant tumours, such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant melanoma, and acute lymphocytic and myelocytic leukaemia. They are also suited for anti-angiogenesis therapy and for the treatment of chronic inflammatory diseases (psoriasis, arthritis). To prevent uncontrolled cell growth on, and for better tolerability of, medical implants, the derivatives can be introduced into or applied to polymeric materials. The compounds provided for in the invention can be used alone or, to achieve additive or synergistic effects, in combination with other principles and substance categories used in tumour therapy.

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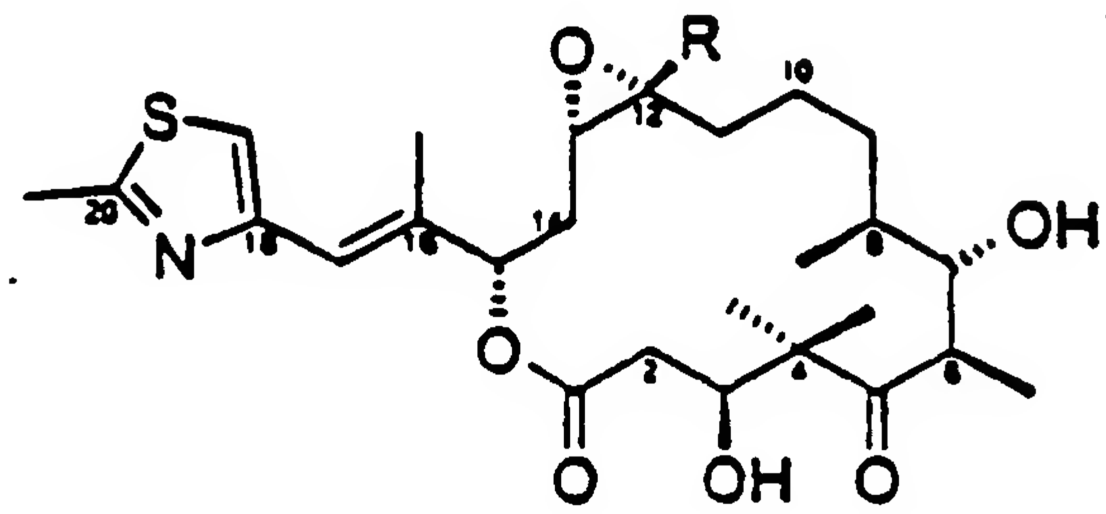
NEW EPOTHILONE DERIVATIVES, METHOD FOR PRODUCING SAME AND THEIR PHARMACEUTICAL USE

Höfle et al. described the cytotoxic effect of the natural substance epothilone A (R = hydrogen) and epothilone B (R = methyl)



epothilone A (R = H), epothilone B (R = CH_3)

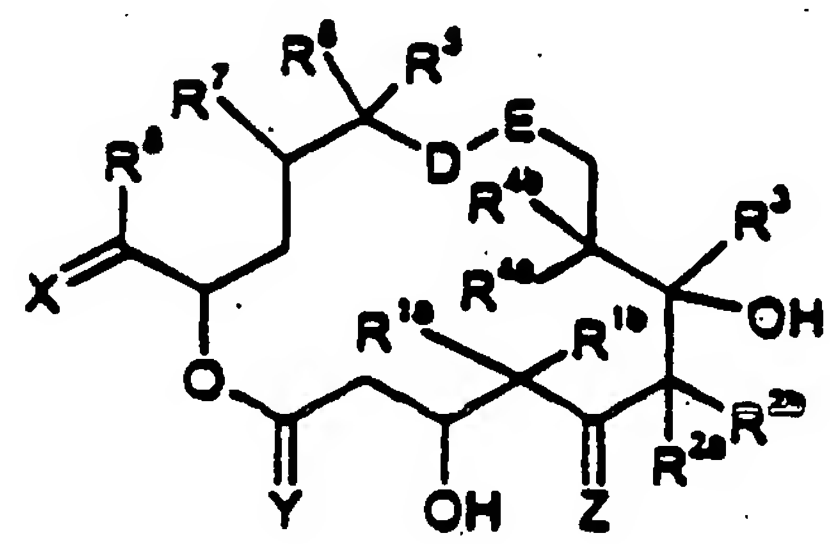
for example, in Angew. Chem. 1996, 108 1671-1673. Because of the in-vitro selectivity to breast and intestinal cell lines and the clearly higher activity in comparison to taxol against P-glycoprotein-forming multiresistant tumor lines, as well as because of the improved physical properties in comparison to taxol, for example, a solubility in water higher by a factor of 30, these new structural classes are of special interest for the development of a drug for the therapy of malignant tumors.

Natural substances are not sufficiently stable either chemically or metabolically for drug development. In order to eliminate these disadvantages, it is necessary to make modifications in the natural substance. Such modifications can only be achieved by total synthesis and require synthesis strategies which permit a broad modification of the natural substance. The goal of the structural changes is also to increase the therapeutic spectrum. This can be done by improving the selectivity of action and/or reduction of adverse toxic side effects and/or by increasing the activity.

The total synthesis of epothilone A is described by Schinzer et al. in Chem. Eur. J. 1996, 2, No. 11, 1477-1483 and in Angew. Chem. 1997, 109, No. 5, p. 543-544). Epothilone derivatives were already described by Höfle et al., in WO 97/19086. These derivatives were prepared starting from natural epothilone A or B. Another synthesis of epothilone and epothilone derivatives was described by Nicolaou et al. in Angew. Chem. 1997, 109, No. 1/2, p. 170-172. The synthesis of epothilone A and B and of some epothilone analogs is described in Nature, Volume 387, 1997, p. 268-272, the synthesis of epothilone A and its derivatives in J. Am. Chem. Soc., Volume 119, No. 34, 1997, p. 7960-7973 as well as the synthesis of epothilone A and B and of some epothilone analogs is described in J. Am. Chem. Soc., Volume 119, No. 34, 1997, p. 7974-7991, also by Nicolaou et al. Again, Nicolaou et al. describe in Angew. Chem. 1997, 109, No. 19, p. 2181-2187 the preparation of epothilone A analogs with combinatorial solid-phase synthesis. Some epothilone B analogs are also described there.

The task of the present invention is to make available new epothilone derivatives which are sufficiently stable both chemically and metabolically for drug development and which are superior to the natural derivatives with regard to the therapeutic spectrum, selectivity of action and/or adverse toxic side effects and/or their activity.

The present invention describes the new epothilone derivatives having general formula I,



I,

where

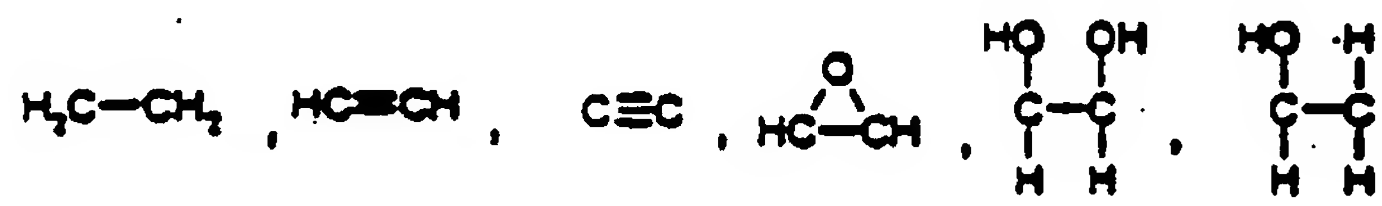
R^{1a}, R^{1b} are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together for a $-(CH_2)_m$ group with m = 2, 3, 4 or 5,

R^{2a}, R^{2b} are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl or together for a $-(CH_2)_n$ group with n = 2, 3, 4 or 5, where, in case

-D-E- stand for $-CH_2-CH_2-$ or Y stands for an oxygen atom, R^{2a}/R^{2b} cannot be hydrogen/methyl,

R^3 stands for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,

R^{4a}, R^{4b} can be the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl or together for a $-(CH_2)_p$ group with p = 2, 3, 4 or 5,

D-E stands a group 

R^5 stands for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,

R^6, R^7 each stand for a hydrogen atom, and together for an additional bond or an oxygen atom,

R^8 stands for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl, all of which may be substituted,

X stands for an oxygen atom, two alkoxy groups OR^{23}, a C_2-C_{10} alkylene-α,ω-dioxy group, which may be straight-chain or branched, H/OR^9 or a $CR^{10}R^{11}$ group,

where

R^{23} stands for a C_1-C_{20} alkyl group,

R^9 stands for hydrogen or a protective group PG^x,

R^{10}, R^{11} are the same or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl group or

R^{10}, R^{11} together with the methylene carbon atom stand for a 5- to 7-membered carbocyclic ring,

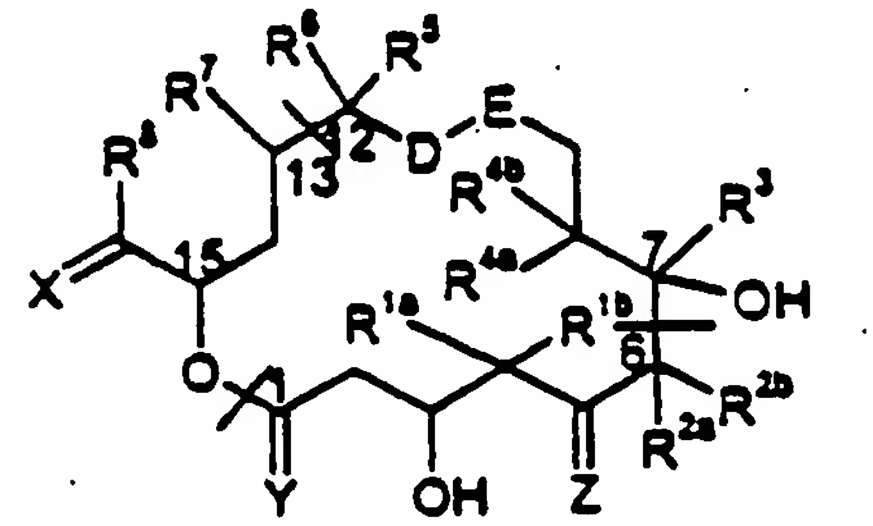
Y stands for an oxygen atom or two hydrogen atoms,

Z stands for an oxygen atom or H/OR^{12},

where

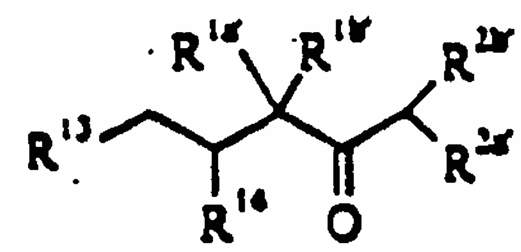
R^{12} is hydrogen or a protective group PG^z.

The preparation of the new epothilone derivatives is based on linking three partial fragments A, B and C. The interfaces are as shown in general formula I'.



I'

A stands for a C_1-C_6 fragment (epothilone numbering) of the general formula



A,

where

$R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$ have the meaning already given for R^{1a}, R^{1b}, R^{2a} and R^{2b}, and

R^{13} stands for CH_2OR^{13a}, CH_2-Hal, CHO, CO_2R^{13b}, COHal,

R^{14} stands for hydrogen, OR^{14a}, Hal, OSO_2R^{14b},

R^{13a}, R^{14a} stand for hydrogen, SO_2 alkyl, SO_2 aryl, SO_2 aralkyl or together for a $(CH_2)_o$ group or together for a $CR^{15a}R^{15b}$ group,

R^{13b}, R^{14b} stand for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl,

R^{15a}, R^{15b} are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl or together for a $-(CH_2)_q$ group,

Hal stands for halogen,

o is 2 to 4,

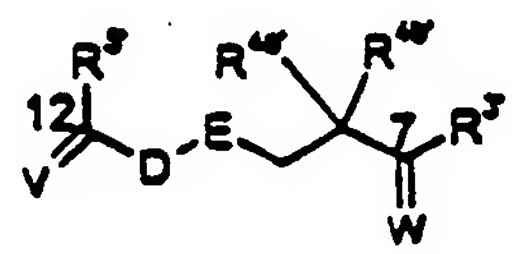
q is 3 to 6,

including all stereoisomers as well as their mixtures

as well as the

free hydroxyl groups in R^{13} and R^{14} are etherified or esterified, the free carbonyl groups in A and R^{13} are ketalized, converted into an enol ether or reduced, as well as the free acid groups in A can be converted into their salts with bases.

B stands for a C7-C12 fragment (epothilone numbering) having the general formula



B

where

$R^{3'}$, $R^{4a'}$, $R^{4b'}$ and $R^{5'}$ have the meanings already given for R^3, R^{4a}, R^{4b} and R^5, and

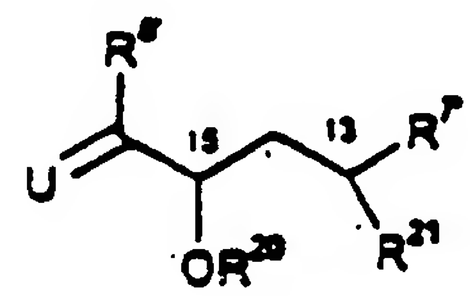
V stands for an oxygen atom, two alkoxy groups OR^{17}, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, or for H/OR^{16},

W stands for an oxygen atom, two alkoxy groups OR^{19}, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched or for H/OR^{18}, where

R^{16}, R^{18} independently of one another stand for hydrogen or a protective group PG^1 and

R^{17}, R^{19} stand for C_1-C_{20} alkyl, independently of one another.

C stands for the C13-C16 fragment (epothilone numbering) of the general formula



C

where

$R^{8'}$ has the meaning already given for R^8 in general formula I and

$R^{7'}$ stands for a hydrogen atom,

R^{20} stands for a hydrogen atom or a protective group PG^2,

R^{21} stands for a hydroxyl group, halogen, a protected hydroxyl group OPG^3, a phosphonium halide group $PPh_3^+Hal^-$ (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate group $P(O)(OQ)_2$ (Q = C_1-C_{10} alkyl or phenyl) or a phosphine oxide group $P(O)Ph_2$ (Ph = phenyl),

U stands for an oxygen, two alkoxy groups OR^{23}, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR^9 or for a group $CR^{10}R^{11}$,

where

R^{23} stands for a C_1-C_{20} alkyl group,

R^9 stands for hydrogen or a protective group PG^3,

R^{10},R^{11} can be the same or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl group or

R^{10},R^{11} together with the methylene carbon atom stand for a 5- to 7-membered carbocyclic ring.

As alkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13b}, R^{14b}, R^{15a}, R^{15b}, R^{17} and R^{23} straight- or branched-chain alkyl groups with 1-20 carbon atoms come into consideration, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, isopentyl, neopentyl, heptyl, hexyl, decyl.
The alkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13b}, R^{14b}, R^{15a}, R^{15b}, R^{17} and R^{23} can be perfluorinated or substituted by 1-5 halogen atoms, hydroxyl group, C_1-C_4 alkoxy groups, C_6-C_{12} aryl groups (which may be substituted by 1-3 halogen atoms).

As the aryl group R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13b}, R^{14b}, R^{15a} and R^{15b}, substituted and unsubstituted carbocyclic or heterocyclic groups with one or more heteroatoms come into consideration, for example, phenyl, naphthyl, furyl, thienyl, pyridyl, pyrazolyl, pyrimidinyl, oxazolyl, pyridazinyl, pyrazinyl, quinolyl, thiazolyl, which may be mono- or polysubstituted by halogen, OH, O-alkyl, CO_2H, CO_2 alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20} alkyl, C_1-C_{20} acyl, C_1-C_{20} acyloxy groups. The heteroatoms in the heteroaryl groups can be oxidized, thus, for example, the thiazole ring can be present in the form of the N-oxide.

The aralkyl groups in R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13b}, R^{14b}, R^{15a} and R^{15b}, may contain up to 14 C atoms in the ring, preferably up to 6 to 10 and 1 to 8 atoms, preferably 1 to 4 atoms in the alkyl chain. As aralkyl groups, for example, benzyl, phenylethyl, naphthylmethyl, naphthylethyl, furylmethyl, thienylethyl, pyridylpropyl come into consideration. The rings may be monosubstituted or polysubstituted by halogen, OH, O-alkyl, CO_2H, CO_2 alkyl, $-NO_2$, $-N_3$, -CN, C_1-C_{20} alkyl, C_1-C_{20} acyl, C_1-C_{20} acyloxy groups. The alkoxy groups contained in X in general formula I, should contain 1 to 20 carbon atoms, where methoxy, ethoxy, propoxy, isopropoxy and t-butyloxy groups are preferred.
As a representative for the protective groups PG, alkyl- and/or aryl-substituted silyl, C_1-C_{20} alkyl, C_4-C_7 cycloalkyl, which may contain an oxygen atom in the ring additionally, aryl, C_7-C_{20} aralkyl, C_1-C_{20} acyl as well as aroyl can be named.

As alkyl, silyl and acyl groups for the protective groups PG, the groups known to the expert in the field come into consideration. Alkyl and silyl groups which can be easily cleaved off from the corresponding alkyl and silyl ethers, for example, methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert.-butyl-dimethylsilyl, tert.-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, para-methoxybenzyl as well as alkylsulfonyl and arylsulfonyl groups are preferred. As acyl groups, for example, formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl or benzoyl, which may be substituted with amino- and/or hydroxyl groups come into consideration.

The acyl groups PG^x or PG^z in R^9 and R^{12} may contain 1 to 20 carbon atoms, but formyl, acetyl, propionyl, isopropionyl and pivalyl groups are preferred.

The index m in the alkylene group, which is formed from R^{1a} and R^{1b}, preferably stands for 2, 3 or 4.

The C_2-C_{10} alkylene-α,ω-dioxy group, which can be used possibly for X, is preferably an ethylene ketal or neopentyl ketal group.

The substituents in the compounds having general formula I can be chosen so that

Y, Z, R^{1a}, R^{1b}, R^{2a} and R^{2b} all can have the meaning given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B, or

R^3, R^{4a}, R^{4b}, D-E, R^5, R^6 and R^7 can all have the meaning given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B, or

R^6, R^7, R^8 and X can all have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B, or

Y, Z, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, D-E, R^5, R^6 and R^7 can all have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B, or

Y, Z, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^6, R^7, R^8, and X can all have the meanings given in general formula I and the rest of the molecule can be identical with the naturally occurring epothilone A or B, or

R^3, R^{4a}, R^{4b}, D-E, R^5, R^6, R^7, R^8 and X can all have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B.

The compounds named below are preferred according to the invention:

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione,
and
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7S,8R,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione
and
(4S,7S,8R,9S,13E,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10S,11R,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10S,11R,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

(1S,3S(E),7S,10S,11R,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10S,11R,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione
and
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((3-pyridyl)-ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((3-pyridyl)-ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione
and
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((4-pyridyl)-ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((4-pyridyl)-ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7-phenyl-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-phenyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-phenyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-7-Benzyl-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-10-Benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-10-Benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,13-tetramethyl-9-trifluoromethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,16-tetramethyl-12-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,16-tetramethyl-12-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,11E/Z,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadeca-11,13-diene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,14E/Z,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(1(R or S),3S,(E),7S,10R,11S,12S,14E/Z,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-11-ine-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ine-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ine-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9-tetramethyl-13-trifluoromethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,12-tetramethyl-16-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,12-tetramethyl-16-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-13-pentafluoroethyl-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-16-pentafluoroethyl-8,8,10,12-tetramethyl-4,17-dioxabicyclo]14.1.0]heptadeca-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-16-pentafluoroethyl-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylene)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8-(1,3-trimethylene)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8-(1,3-trimethylene)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione

(4S,7R,8S,9S,11E/Z,13(E or Z),16S(E))-4,8-Dihydroxy-13-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadeca-11,13-diene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,14E/Z,16R)-7,11-Dihydroxy-16-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,14E/Z,16S)-7,11-Dihydroxy-16-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(4S,7R,8S,9S,11E/Z,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-13-propyl-5,5,7,9-tetramethyl-cyclohexadeca-11,13-diene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,14E/Z,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-propyl-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,14E/Z,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-propyl-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(4-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(4-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(4-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

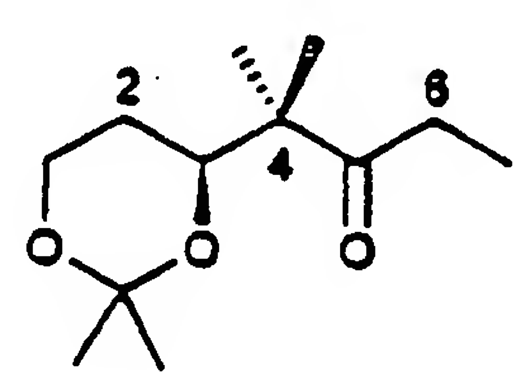
(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-6-one

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec[sic]-9-one

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec[sic]-9-one

Preparation of partial fragments A:

It is known that the compound having the following formula

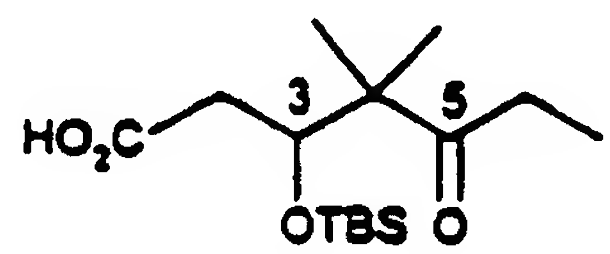


can be used for the synthesis of the C1-C6 fragment (epothilone numbering) of epothilone A (Schinzer et al., Chem. Eur. J. 1996, 2, No. 11, 1477-1482; Schinzer et al., Angew. Chem. 1997, 109, No. 5, p. 543-544).

This synthesis has the disadvantage that the total yield is very low with 10.5%, the necessary introduction of the chirality on the C-atom 3 requires the synthesis of an expensive, chemically unstable chiral auxiliary which must be used in equimolar amounts and cannot be recovered and thus the achieved optical induction is incomplete, namely approximately 80%ee.

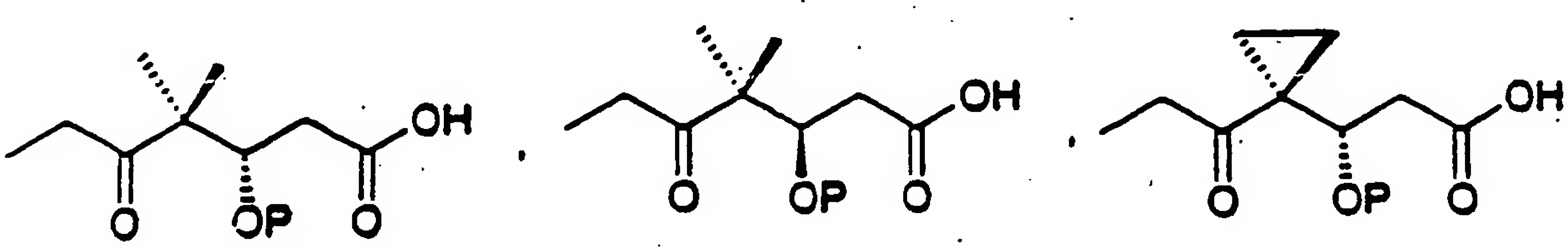
However, for a synthesis that can be utilized industrially, high yields and high optical purity are necessary.

In Angew. Chem. 1997, 109, No. 1/2, p. 170-172, a synthesis is described by Nicolaou et al., for a (C1-C6) unit with a carboxyl group at C-1, and which can be used for the synthesis of epothilone or epothilone derivatives,



(TBS = *tert.*-butyldimethylsilyl). The stereochemistry at C3 is controlled by the reaction with the Brown reagent allylisopinocamphenylborane (+)-Ipc_2B(allyl), which must be used in equimolar amounts in the reaction and cannot be recovered.

Similarly, the use of this unit for the synthesis of epothilone A and B and for some epothilone analogs was described by Nicolaou et al., in Nature, Volume 387, 1997, p. 268-272, in J. Am. Chem. Soc., Volume 119, No. 34, 1997, p. 7960-7973 for the synthesis of epothilone A and its derivatives, as well as in J. Am. Chem. Soc., Volume 119, No. 34, 1997, p. 7974-7991 for the synthesis of epothilone A and B and of some epothilone analogs. Similarly, Nicolaou et al. described in Angew. Chem. 1997, 109, No. 19, p. 2181-2187 the preparation of epothilone A analogs with combinatorial solid-state synthesis. This source also shows epothilone B analogs. The following compounds are used as C1-C6 building blocks:



P = TBS

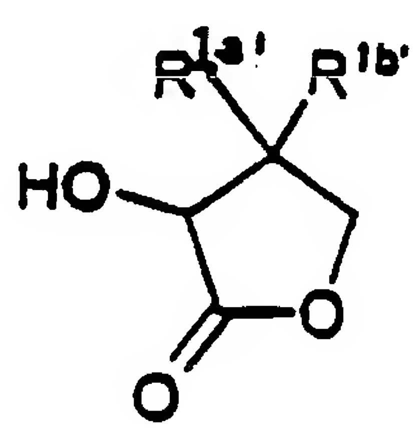
For industrially useful synthesis, it is advantageous when the synthesis can be carried out without expensive chiral auxiliaries.

Therefore, the task was to find a suitable synthesis which gives high yields, which provides the desired product in high optical purity and which can be achieved without the use of expensive chiral auxiliaries.

In addition, the new synthesis should permit a broad variation of substituents in this unit and thus also in the epothilone derivatives to be produced from it. .

The partial fragments (synthesis building blocks) of general formula A can be prepared easily as starting material from

a) a pantolactone having general formula IIa



II a

where

$R^{1a'}$, $R^{1b'}$ each stand for a methyl group

or

b) for a malonic acid dialkyl ester having general formula XXVIII

XXVIII

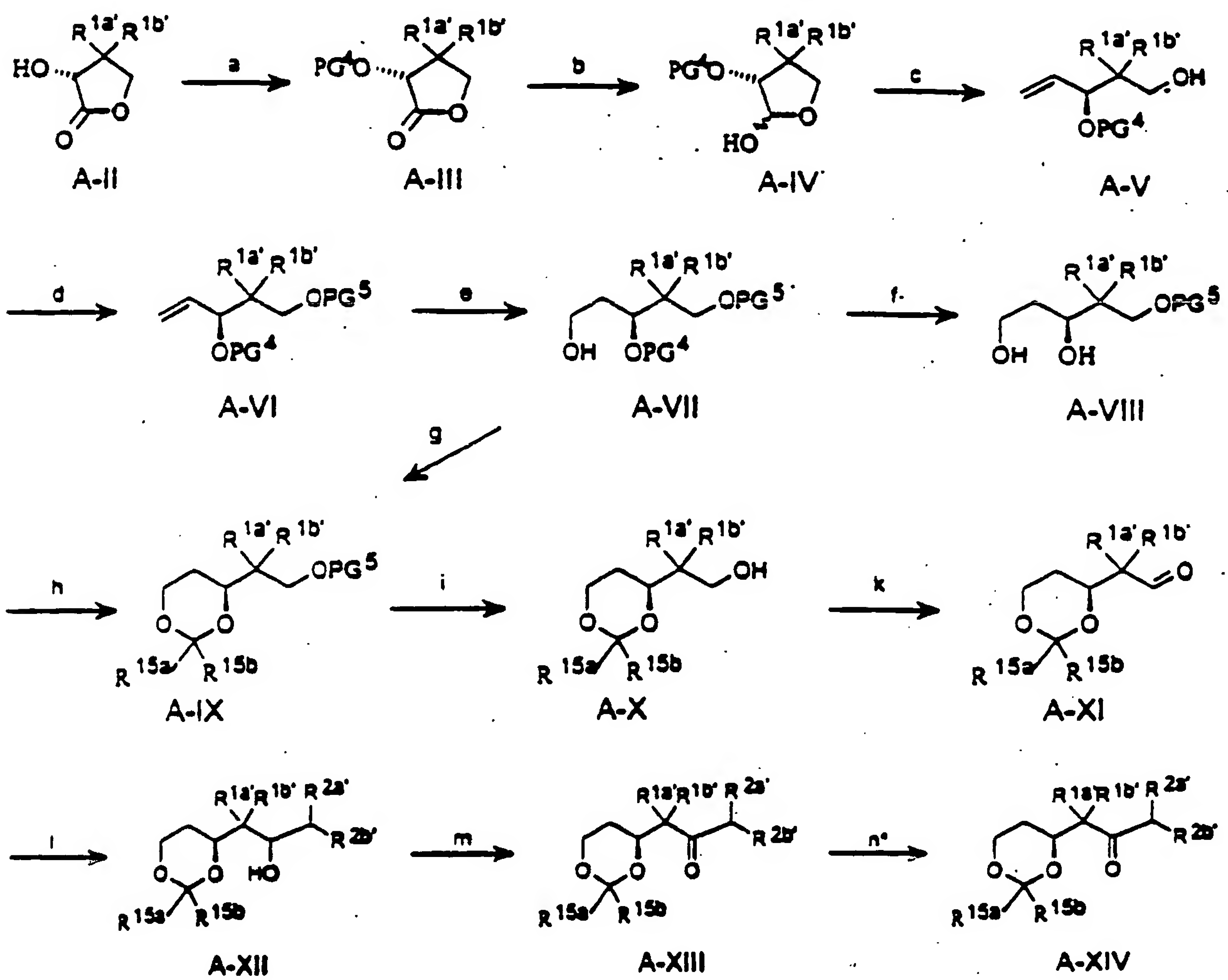
where

$R^{1a'}$ and $R^{1b'}$ have the meaning given in general formula A and the alkyl groups stand for a C_1-C_{20} alkyl, C_3-C_{10} cycloalkyl or C_4-C_{20} alkylcycloalkyl, independently of one another.

The partial fragments A, in which $R^{1a'}$ = $R^{1b'}$ = methyl, can be prepared from inexpensive pantolactone efficiently, with an optical purity of > 98%ee.

The synthesis is described in the following Scheme 1 using the example of D-(-)-pantolactone. Starting from L-(+)-pantolactone, one obtains the corresponding enantiomeric compounds A-II to A-XIV, ent-A-II to ent-A-XIV and from the racemic DL-pantolactone, the corresponding racemic compounds rac-A-II to rac-A-XIV:

Scheme 1



*: only, in case $R^{2a'}$ or $R^{2b'}$ is equal to hydrogen in A-XIII

Step a (A-II → A-III):

The free hydroxyl group of pantolactone (A-II) is protected according to methods known to the expert in the field. As protective group PG^4, the protective groups known to the expert in the field come into consideration, for example, methoxymethyl-, methoxyethyl-, ethoxyethyl-, tetrahydropyranyl-, tetrahydrofuranyl-, trimethylsilyl-, triethylsilyl-, tert.-butyldimethylsilyl-, tert.-butyldiphenylsilyl-, tribenzylsilyl-, triisopropylsilyl-, benzyl, para-nitrobenzyl-, para-methoxybenzyl-, formyl-, acetyl-, propionyl-, isopropionyl-, pivalyl-, butyryl- or benzoyl group.

A survey can be found, for example, in "Protective Groups in Organic Synthesis", Theodora W. Green, John Wiley and Sons).

Those protective groups are preferred which can be cleaved under acidic reaction conditions, for example, the methoxymethyl-, tetrahydropyranyl-, tetrahydrofuranyl-, trimethylsilyl group.

The tetrahydropyranyl group is especially preferred.

Step b (A-III → A-IV):

The protected lactone A-III is reduced to the lactol A-IV. Aluminum hydrides, modified in their reactivity, are suitable as reducing agent, for example, diisobutylaluminum hydride. The reaction is carried out in an inert solvent, such as toluene, preferably at low temperatures.

Step c (A-IV → A-V):

The lactol A-IV is opened to the hydroxyolefin A-V by adding a C-atom. The methods known to the expert in the field are suitable for doing this, for example, the olefination according to Tebbe, the Wittig- or Wittig/Horner reaction, the addition of an organometallic compound while cleaving off water. The Wittig reaction using methyltriarylphosphonium halides is preferred, for example, methyltriphenylphosphonium bromide with strong bases, such as n-butyllithium, potassium-tert.-butanolate, sodium ethanolate, sodium hexamethyldisilazane; n-butyllithium is preferred as base.

Step d (A-V → A-VI):

The free hydroxyl group in A-V is protected according to methods known to the expert. The protective groups known to the expert come into consideration as protective group PG^5, as they were already named before for PG^4 in Step a (A-II, A-III).

Those protective groups are preferred which can be cleaved under reaction of fluoride, for example, the trimethylsilyl, tert.-butyldimethylsilyl, tert.-butyldiphenylsilyl, tribenzylsilyl-, triisopropylsilyl group.

The tert.-butyldimethylsilyl, triisopropylsilyl- and tert.-butyldiphenylsilyl groups are especially preferred.

Step e (A-VI → A-VII):

In A-VI, water is added to the double bond according to the anti-Markovnikov reaction. For this purpose, the methods known to the expert are suitable, for example, the reaction with boranes, their subsequent oxidation to the corresponding boric acid esters and their saponification. For example, the borane tetrahydrofuran complex, the borane dimethylsulfide complex, 9-borabicyclo[3.3.1]nonane are preferred as boranes in an inert solvent, for example, tetrahydrofuran or diethyl ether. As oxidizing agent, preferably hydrogen peroxide is used and sodium hydroxide is preferably used for the saponification of the boric acid ester, preferably an alkali hydroxide, such as sodium hydroxide.

Step f (A-VI → A-VII):

The protective group PG^4 introduced in Step a) is now cleaved off, according to methods known to the expert. If this is an acidic cleavable protective group, then dilute mineral acids in aqueous-alcoholic solutions, the use of catalytic amounts of acids, for example, para-toluenesulfonic acid, para-toluenesulfonic acid pyridinium salt, camphorsulfonic acid in alcoholic solutions, preferably, in ethanol or isopropanol, are suitable.

Step g (A-VII → A-IX):

A common protection of both alcohol functions of the mono-protected 1,3-diol in A-VII is possible under acid catalysis, by direct ketalization with a carbonyl compound having the general formula R^{15a}-CO-R^{15b}, or by transketalization with a ketal having the general formulas, R^{15a}-$C(OC_2H_5)_2$-R^{15b}, R^{15a}-$C(OC_2H_4)_2$-R^{15b}, R^{15a}-$C(OCH_2C(CH_3)_2CH_2O)$-R^{15b}, where R^{15a} and R^{15b} have the meanings given above. As acids, the acids already mentioned in Step

f) are suitable and para-toluenesulfonic acid, optionally with the addition of copper(II) or cobalt(II) salts, for example, copper(II) sulfate, is preferred.

Step h (A-VIII → A-IX):

A protection of both alcohol functions of the 1,3-diol in A-VIII is possible under acid catalysis by direct ketalization with a carbonyl compound having the general formula R^{15a}-CO-R^{15b}, or by transketalization with a ketal having the general formulas R^{15a}-$C(OC_2H_5)_2$-R^{15b}, R^{15a}-$C(OC_2H_4)_2$-R^{15b}, R^{15a}-$C(OCH_2C(CH_3)_2CH_2O)$-R^{15b} where R^{15a} and R^{15b} have the meaning given above. Transketalization is preferred, especially with 2,2-dimethoxypropane. As acids, the acids named under Step f) are suitable, and camphorsulfonic acid is preferred.

Step i (A-IX → A-X):

The protective group, PG^5, introduced in Step d) is now cleaved off according to methods known to the expert. If this is a silyl ether, then reaction with fluorides, for example, with tetrabutylammonium fluoride, the hydrogen fluoride pyridine complex, potassium fluoride or the use of dilute mineral acids, the use of catalytic amounts of acids, for example, para-toluenesulfonic acid, para-toluenesulfonic acid-pyridinium salts, camphorsulfonic acid in alcoholic solutions, preferably in ethanol or isopropanol, is suitable the cleavage.

Step k (A-X → A-XI):

The oxidation of the primary alcohol in A-X to the aldehyde is carried out according to the methods known to the expert. For example, let us mention oxidation with pyridinium chlorochromate, pyridinium dichromate, chromium trioxide-pyridine complex, the oxidation according to Swern or related methods, for example, using oxalyl chloride in dimethylsulfoxide, the use of the Dess-Martin periodinans, the use of nitrogen oxides, for example, N-methylmorpholino-N-oxide in the presence of suitable catalysts, such as tetrapropylammonium perruthenate in inert solvents should be mentioned. The oxidation according to Swern, as well as with N-methylmorpholino-N-oxide using tetrapropylammonium perruthenate are preferred.

Step l (A-XI → A-XII):

The reaction of the aldehydes A-XI to alcohols having the formula A-XII is done with organometallic compounds having the general formula M-$CHR^{2a'}R^{2b'}$, where M stands for an alkali metal, preferably lithium, or a divalent metal MX, where X represents a halogen and the groups $R^{2a'}$ and $R^{2b'}$ have the meanings already given above. Magnesium and zinc are preferred as divalent metals and chlorine, bromine and iodine are preferred as halogen X.

Step m (A-XII → A-XIII):

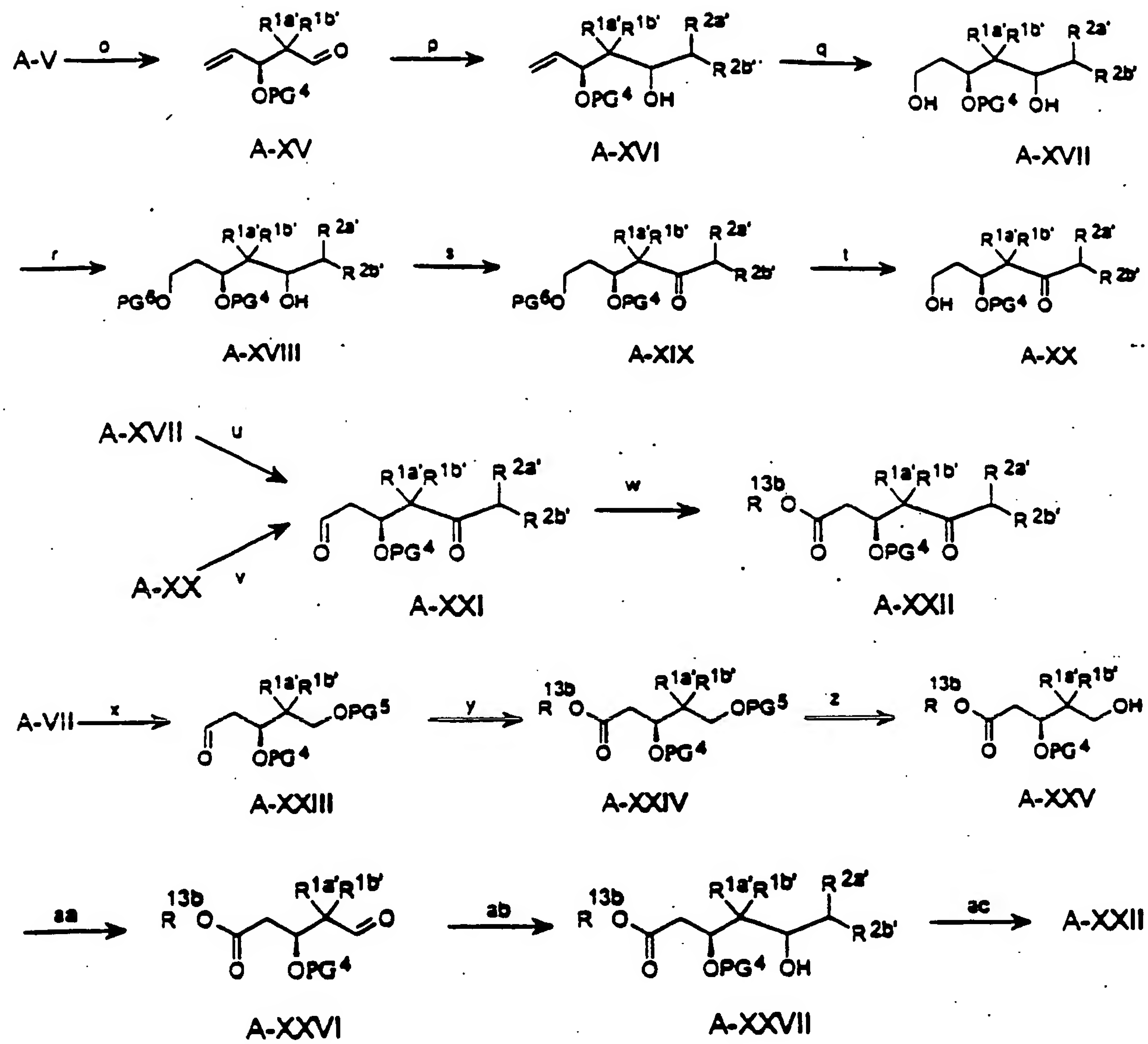
The oxidation of the secondary alcohol in A-XII to the ketone A-XIII is carried out under the conditions mentioned (in Step k). Oxidation with N-methylmorpholino-N-oxide using tetrapropylammonium perruthenate is preferred.

Step n (A-XIII → A-XIV):

For the case where $R^{2a'}$ in A-XIII is equal to hydrogen, there is a possibility to introduce for this a second group $R^{2a'}$ under the conditions named above, with the exception of hydrogen. For this purpose, the use of strong bases, for example, lithium diisopropylamide, the ketone in A-XIII is introduced into the enolate and reacted with a compound having general formula X-$R^{2a'}$, where X represents a halogen. Chlorine, bromine and iodine is preferred as halogen X. The route described above can also be used for synthesizing the C1-C6 epothilone building blocks which contain a carboxylic acid or their ester at C-1 ($R^{13}=CO_2R^{13b}$ in A).

The synthesis of the building block A-XXII is described in the following Scheme 2 using the intermediate step A-V derived from D-(-)-pantolactone as example. Starting from L-(+)-pantolactone, one obtains the corresponding enantiomeric compounds A-V to A-XXVII, ent-A-V to ent-A-XXVII and from the racemic DL pantolactone, one obtains the corresponding racemic compounds rac-A-V to rac-A-XXVII:

Scheme 2



Step o (A-V → A-XV):

The oxidation of the primary alcohol in A-V to the aldehyde A-XV is done under the conditions given in Step k). The oxidation method according to Swern is preferred.

Step p (A-XV → A-XVI):

The reaction on the aldehyde A-XV to the alcohols having formula A-XVI is done with organometallic compounds having the general formula M-CHR$^{2a'}$R$^{2b'}$, where M stands for an

alkali metal, preferably lithium or a divalent metal MX, where X represents a halogen and the groups $R^{2a'}$ and $R^{2b'}$ have the meanings given above. As a divalent metal, magnesium and zinc are preferred, while chlorine, bromine and iodine are preferred as halogen X.

Step q (A-XVI → A-XVII):

Water is added to the double bond in A-XVI according to the anti-Markovnikov reaction. For this purpose, the methods described under e) are suitable.

Step r (A-XVII → A-XVIII):

The free hydroxyl group in A-XVII is protected according to the methods known to the expert. As the protective group PG^6, the protective groups known to the expert are suitable, as already named before for PG^4 is Step a) (A-II → A-III), come into consideration. Preferred are those protective groups which can be cleaved under basic or hydrogenolytic reaction conditions, for example, benzyl, para-nitrobenzyl, acetyl, propionyl, butyryl, and benzoyl groups.

The benzoyl group is especially preferred.

Step s (A-XVIII → A-XIX):

The oxidation of the secondary alcohol in A-XVII to the ketone A-XIX is done according to the conditions given in Step k). Oxidation with N-methylmorpholino-N-oxide using tetrapropylammonium perruthenate is preferred.

Step t (A-XIX → A-XX):

The protective group PG^6 in XIX is now cleaved selectively. If it is a protective group that can be cleaved with hydrogenolysis, then preferably it is hydrogenated in the presence of palladium or platinum catalysts in inert solvents, for example, ethyl acetate or ethanol. If it is a protective group that can be cleaved with a base, then preferably saponification with carbonates in alcoholic solution, for example, with potassium carbonate in methanol, saponification with aqueous solutions of alkali hydroxides, for example, lithium hydroxide or sodium hydroxide are used in organic solvents that are miscible with water, for example, methanol, ethanol, tetrahydrofuran or dioxane.

Step u (A-XVII → A-XXI):

The oxidation of the alcohols in A-XVII to the ketoaldehyde A-XXI is done under the conditions already named in Step k). Oxidation with N-methylmorpholino-N-oxide and use of tetrapropylammonium perruthenate as well as the method according to Swern are preferred.

Step v (A-XX → A-XXI):

The oxidation of the primary alcohol in A-XX to the ketoaldehyde A-XXI occurs according to the conditions named in Step k). Oxidation with N-methylmorpholino-N-oxide using tetrapropylammonium perruthenate is preferred.

Step w (A-XXI → A-XXII):

The oxidation of the aldehyde in A-XXI to the carboxylic acid A-XXII (R^{13b} = hydrogen) is done according to methods known to the expert. For example, let us mention the oxidation according to Jones, the oxidation with potassium permanganate, especially in an aqueous system of tert.-butanol and sodium dihydrogen phosphate, oxidation with sodium chlorite in aqueous tert.-butanol optionally in the presence of a chlorine-capturing agent, such as, for example, 2-methyl-2-butene.

The oxidation of the aldehyde in A-XXI to the ester A-XXII, where R^{13b} has the meanings given above and is not equal to hydrogen, can be carried out, for example, with pyridinium dichromate and the desired alcohol HO-R^{13b} in an inert solvent, such as dimethylformamide.

Step x (A-VII → A-XXIII):

The oxidation of the primary alcohol in A-VII to the aldehyde A-XXIII is done under the conditions named in Step k). Oxidation with N-methylmorpholino-N-oxide using tetrapropylammonium perruthenate as well as the method according to Swern are preferred.

Step y (A-XXIII → A-XXIV):

The oxidation of the aldehyde A-XXIII to the carboxylic acid or to its ester A-XXIV is done according to the conditions already described under w).

Step z (A-XXIV → A-XXV):

The protective group PG^5 introduced under Step d) is cleaved as described in Step i).

Step aa (A-XXV → A-XXVI):

The oxidation of the primary alcohol in A-XXV to the aldehyde A-XXVI is done according to the conditions given under Step k). Oxidation with N-methylmorpholino-N-oxide using tetrapropylammonium perruthenate as well as the method according to Swern are preferred.

Step ab (A-XXVI → A-XXVII):

The reaction of the aldehyde A-XXVI to alcohols having formula A-XXVII is done under the conditions named in Step l).

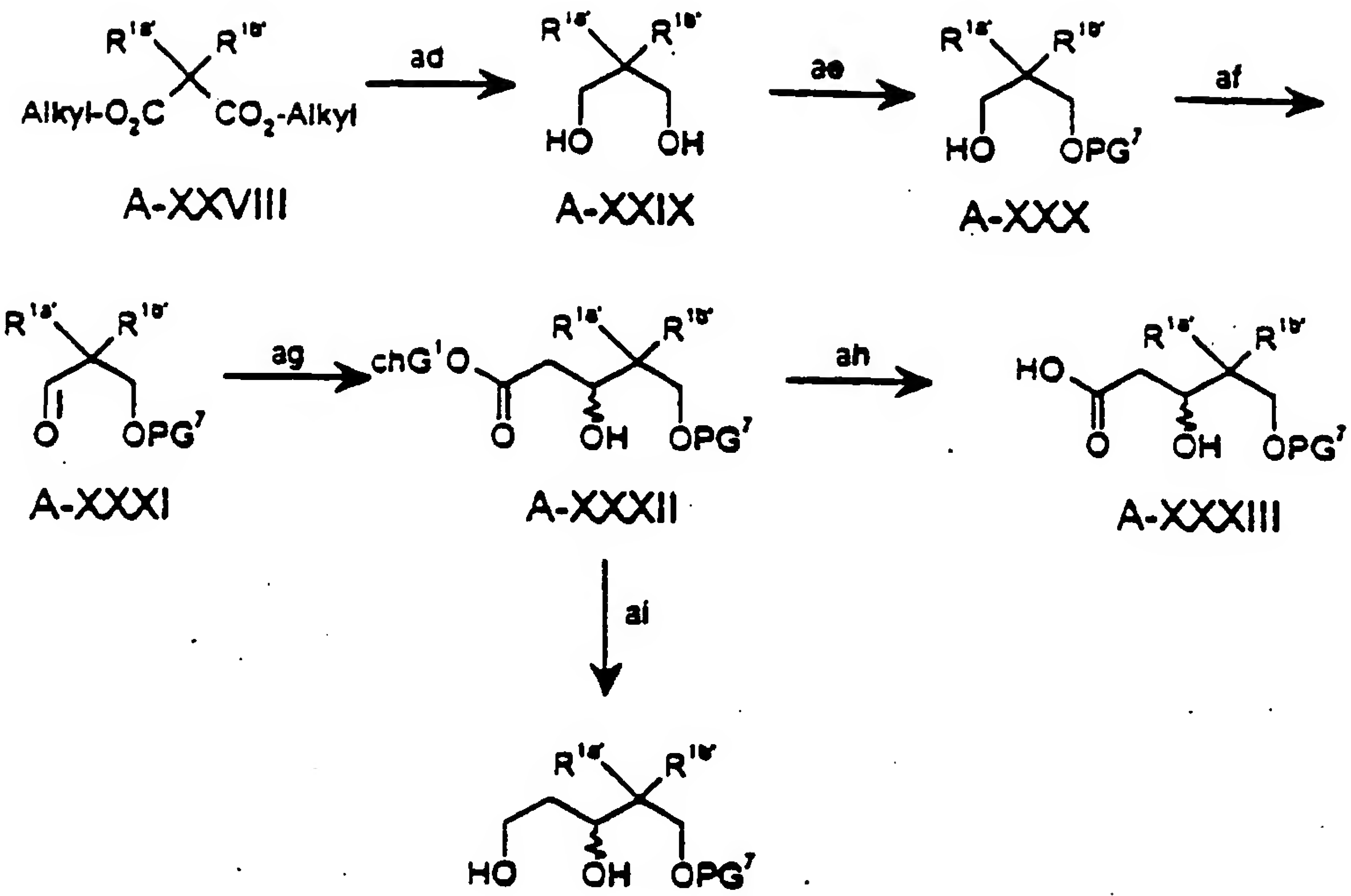
Step ac (A-XXVII → A-XXII):

The oxidation of the secondary alcohol in A-XXVII to the ketone A-XXII is done according to the conditions given in Step k). Oxidation with N-methylmorpholino-N-oxide using tetrapropylammonium perruthenate is preferred.

The compounds having formula A, in $R^{1a'}$ and $R^{1b'}$ can have all the meanings given in general formula A, but, furthermore, they can be prepared from inexpensive or easily accessible malonic acid dialkyl esters in an efficient manner in high optical purity.

The synthesis is described according to the following Scheme 3:

Scheme 3



A-VIII or ent-A-VIII

Step ad (A-XXVIII → A-XXIX):

Correspondingly substituted malonic acid ester derivatives A-XXVIII, which are either commercially available or can be prepared from malonic acids or their alkyl esters according to methods known to the expert, are reduced to diols A-XXIX. For this purpose, reducing agents known to the expert, such as, for example, diisobutylaluminum hydride, complex metal hydrides, such as, for example, lithiumaluminum hydrides, are suitable.

Step ae (A-XXIX → A-XXX):

A free hydroxyl group in A-XXIX is protected selectively according to methods known to the expert. As protective group PG^7, protective groups known to the expert as they were already named for PG^4 in Step a) (A-II → A-III) come into consideration.
Silicon-containing protective groups are preferred.

Step af (A-XXX → A-XXXI):

The oxidation of the remaining primary hydroxyl group in A-XXX to the aldehyde A-XXXI is done under the conditions given under Step k). Oxidation with N-methylmorpholino-N-oxide using tetrapropylammonium perruthenate, the use of pyridinium chlorochromate, pyridinium dichromate as well as the method according to Swern are preferred.

Step ag (A-XXXI → A-XXXII):

The aldehyde A-XXXI is reacted with an ester of acetic acid $chG^1OC(O)CH_3$, where chG^1 is a chiral auxiliary, in the sense of an aldol reaction. The compounds $chG^1OC(O)CH_3$ are used in the optically pure form in the aldol reaction. The nature of the chiral auxiliary determines if the aldol reaction will be run with high diastereoselectivity or gives a diastereomer mixture which can be separated by physical methods. A review of comparable diastereoselective aldol reactions is found in Angew. Chem. 99 (1987), 24-37. As chiral auxiliaries chG^1-OH, for example, optically pure 2-phenylcyclohexanol, pulegol, 2-hydroxy-1,2,2-triphenylethanol, 8-phenylmenthol are suitable.

Step ah (A-XXXII → A-XXXIII):

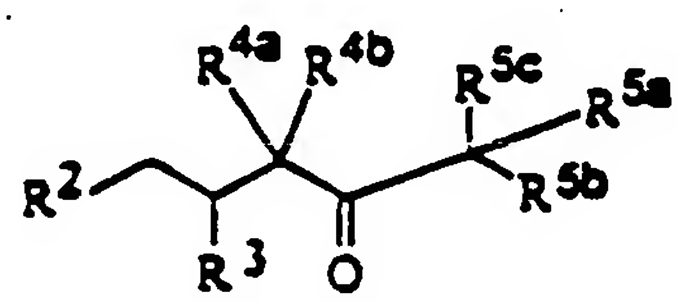
The diastereoisomeric pure compounds A-XXXII can then be converted into pure enantiomeric compounds of the type A-XXXIII or ent-A-XXXIII by methods known to the expert by saponification of the ester group and simultaneous liberation of the reusable chiral helping components chG^1-OH. Carbonates in alcoholic solution, for example, potassium carbonate in methanol, aqueous solutions of alkali hydroxides, for example, lithium hydroxide or sodium hydroxide using organic, water-miscible solvents, for example, methanol, ethanol, tetrahydrofuran or dioxane are suitable for the saponification.

Step ai (A-XXXII → A-VIII):

Alternatively to Step ah), the chiral auxiliary can also be removed reductively. In this way, the pure enantiomeric compounds of the type A-VIII or ent-A-VIII are obtained. The reduction can be carried out according to methods known to the expert. For example, diisobutylaluminum hydride and complex metal hydrides, for example, lithiumaluminum hydride come into consideration as reducing agents.

The compounds A-VIII to ent-A-VIII can be converted to the compounds of the type A-XIII or ent-A-XIII as described before. Correspondingly, compounds of the type A-XXXIII or

ent-A-XXXIII can be converted to compounds of the type A-XXII or ent-A-XXII by the method described above.
Alternatively to the route outlined above, the sequence can also be carried out without the use of a chiral auxiliary group chG^1. In this way then, racemic compounds of the type rac-A-VIII or rac-A-XXXIII are obtained through the corresponding racemic precursors. These mixtures can again be separated by methods known to the expert for the resolution of racemates, for example, chromatography on chiral columns. However, the continuation of the synthesis can also be performed with the racemic mixtures.
Thus, the present invention is also concerned with a method for the preparation of compounds having general formula A, which is characterized by the fact that
a) a pantolactone having general formula IIa or
b) a malonic acid dialkyl ester having general formula XXVIII
is used as starting material.
Thus, in addition, the present invention is concerned with the new C1-C6 epothilone building blocks having general formula A'



A'

where

R^2	stands for CH_2OR^{2a}, CHO, CO_2R^{2b}, COX,
R^{2a}, R^{2b}	stands for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl,
R^3	stands for hydrogen, OR^{3a}, X, OSO_2R^{3b},
R^{3a}	stands for hydrogen or together with R^{2a} for a $-(CH_2)_n$ group or a $CR^{6a}R^{6b}$ group,
R^{3b}	stands for C_1-C_4 alkyl, aryl,
X	is halogen,
n	is 2 to 4,
R^{6a}, R^{6b}	are the same or different and stand for C_1-C_8 alkyl, C_6-C_{10} aryl, or together for a $-(CH_2)_o$ group,
o	is 3 to 6,
R^{6a}	additionally can mean hydrogen,

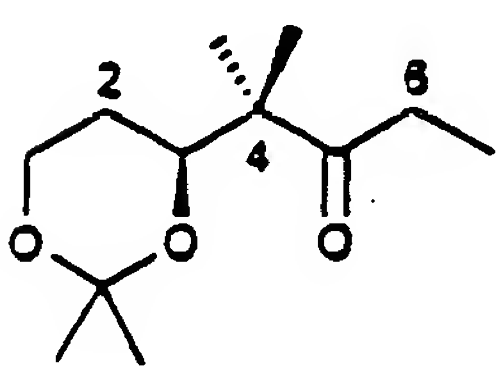
R^{4a}, R^{4b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a -$(CH_2)_m$ group,
m	is 2 to 5,
R^{5a}, R^{5b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a -$(CH_2)_p$ group,
p	is 2 to 5,
R^{5c}	is hydrogen,

including all stereoisomers as well as their mixtures

as well as

the free hydroxyl groups in R^2 and R^3 can be etherified or esterified, the free carbonyl groups in A and R^2 can be ketalized, converted into an enol ether or reduced, as well as the free acid groups in A can be converted to their salts with bases,

with the exception of the compounds



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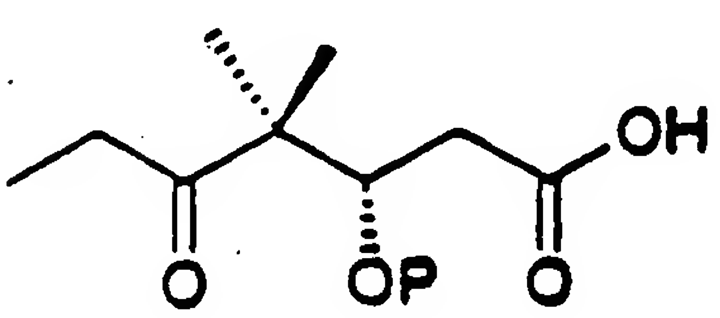

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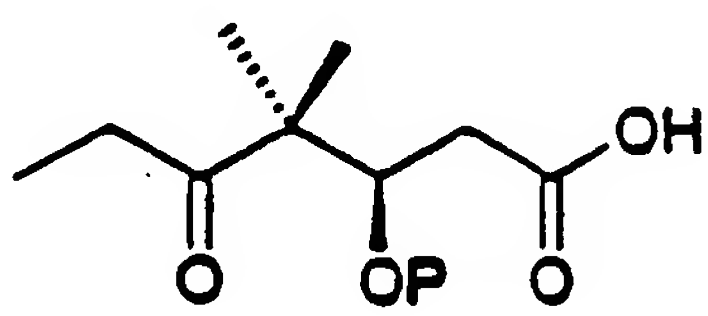

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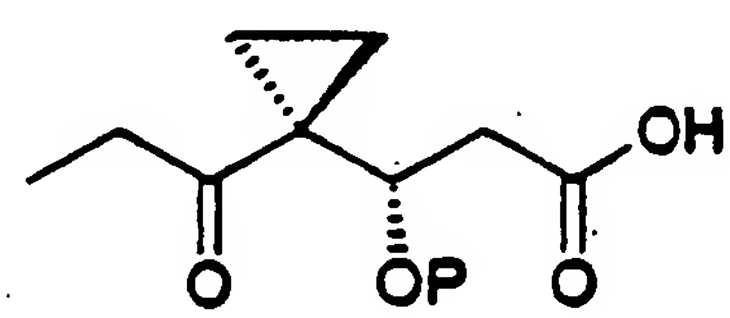
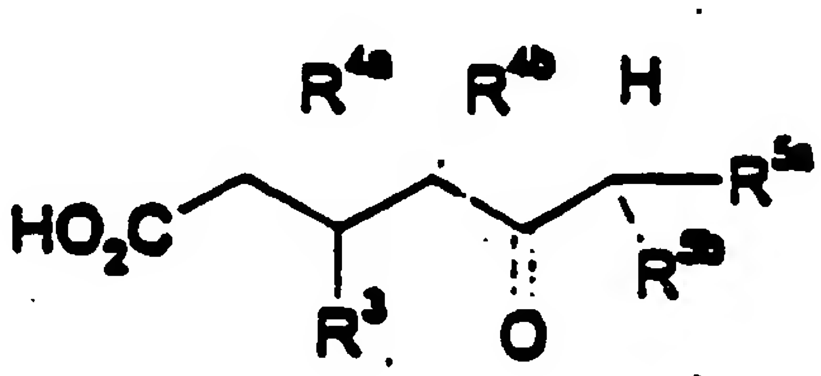


P = TBS

Furthermore, it was found that synthesis building blocks having general formula A"



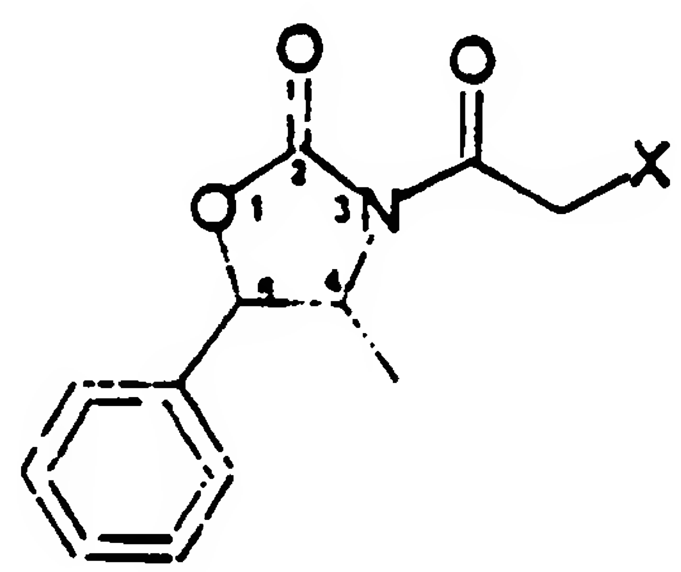
A"

where

R^3	is OR^{3a} and
R^{3a}	stands for hydrogen or a protective group PG
R^{4a}, R^{4b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a $-(CH_2)_m$ group,
m	is 2 to 5,
R^{5a}, R^{5b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a $-(CH_2)_p$ group,
p	is 2 to 5,

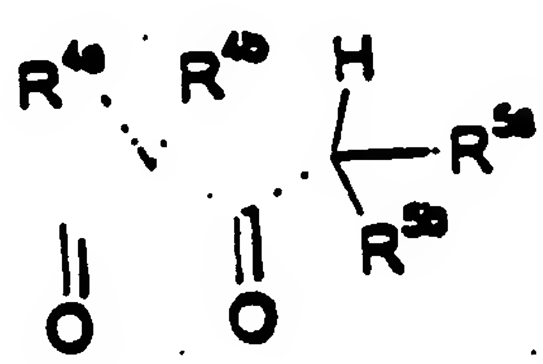
including all stereoisomers as well as mixtures thereof
as well as
the free carbonyl groups in I can be ketalized,

can be prepared easily by reaction of a compound having general formula II



II

where
X is a chlorine or bromine atom and the 2-oxazolidinone ring has either the (4R,5S)- or (4S,5R)-conformation,
with a compound having general formula III.



III

where

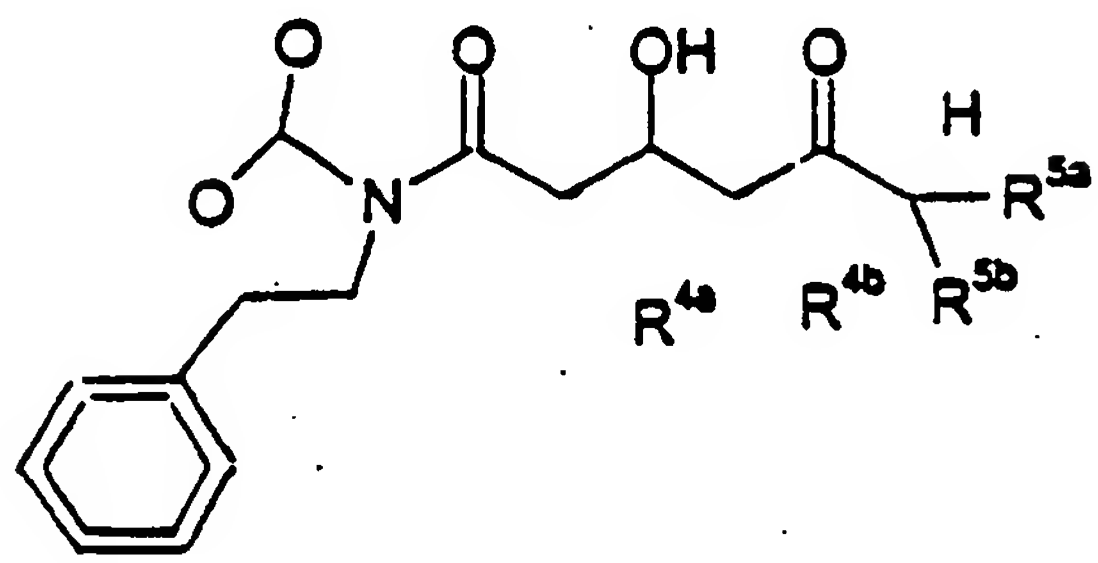
R^{4a}, R^{4b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a $-(CH_2)_m$ group,

m is 2 to 5,

R^{5a}, R^{5b} are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a -$(CH_2)_p$ group,

p is 2 to 5,

to a compound having general formula IV



IV

where
the 2-oxazolidinone ring (4R,5S)- and the 3'-carbon atom have the R conformation or the 2-oxazolidinone ring (4S,5R)- and the 3'-carbon atom have the S conformation,

as well as after protection of the 3'-hydroxyl group in IV with a protective group PG, and by cleaving off the oxazolidinone group and optionally cleaving off the protective group PG.

The reaction of a compound having general formula II with a compound having general formula III can be carried out after conversion of the compound having general formula II into a metal enolate by insertion of a metal or metal salt into the carbon-halogen bond of the compound having general formula II.

As a metal or metal salt, generally all metals or metal salts come into consideration which are known to the expert and are suitable for a Reformatzky reaction (see, for example, A. Fürstner, Synthesis 1989, 571-590).
According to the invention, preferably chromium(II) chloride is used.

When cleaving off from the compounds having general formula IV, the oxazolidone ring retains its optical activity almost quantitatively and without any loss.

As alkyl groups R^{4a}, R^{4b}, R^{5a} and R^{5b}, straight-chain or branched-chain alkyl groups with 1 to a maximum of 10 carbon atoms come into consideration, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, isopentyl, neopentyl, heptyl, hexyl, decyl.

The alkyl groups R^{4a}, R^{4b}, R^{5a} and R^{5b} can be perfluorinated or substituted by 1-5 halogen atoms, hydroxyl groups, C_1-C_4 alkoxy groups and C_6-C_{12} aryl groups (which can be substituted by 1-3 halogen atoms).

The aralkyl groups in R^{4a}, R^{4b}, R^{5a} and R^{5b} may contain up to 14, preferably 6 to 10 C-atoms in the ring and 1 to 8, preferably 1 to 4 atoms in the alkyl chain. As aralkyl groups, for example, benzyl, phenylethyl, naphthylmethyl, naphthylethyl, furylmethyl, thienylethyl, pyridylpropyl groups come into consideration as aralkyl groups. The rings may be mono- to trisubstituted by halogen, OH, O-alkyl, NH_2, CO_2H, CO_2-alkyl, $-NO_2$, $-N_3$, -CN, C_1-C_{20} alkyl, C_1-C_{20} acyl, C_1-C_{20} acyloxy groups.

As protective group PG, all groups known to the expert as such protective groups come into consideration. Silyl-containing protective groups, such as, for example, trimethylsilyl, triethylsilyl, tert.-butyldimethylsilyl, tert.-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl groups are preferred.
A review of protective groups can be found, for example, in "Protective Groups in Organic Synthesis", Theodora W. Green, John Wiley and Sons.

Halogen means fluorine, chlorine, bromine and iodine.

The compounds needed for the method according to the invention, having general formula II are accessible by acetylation of (4R,5S)- or (4S,5R)-4-methyl-5-phenyl-2-oxazolidinone with bromine or chloroacetyl chloride in the presence of a strong base, for example, n-butyllithium.

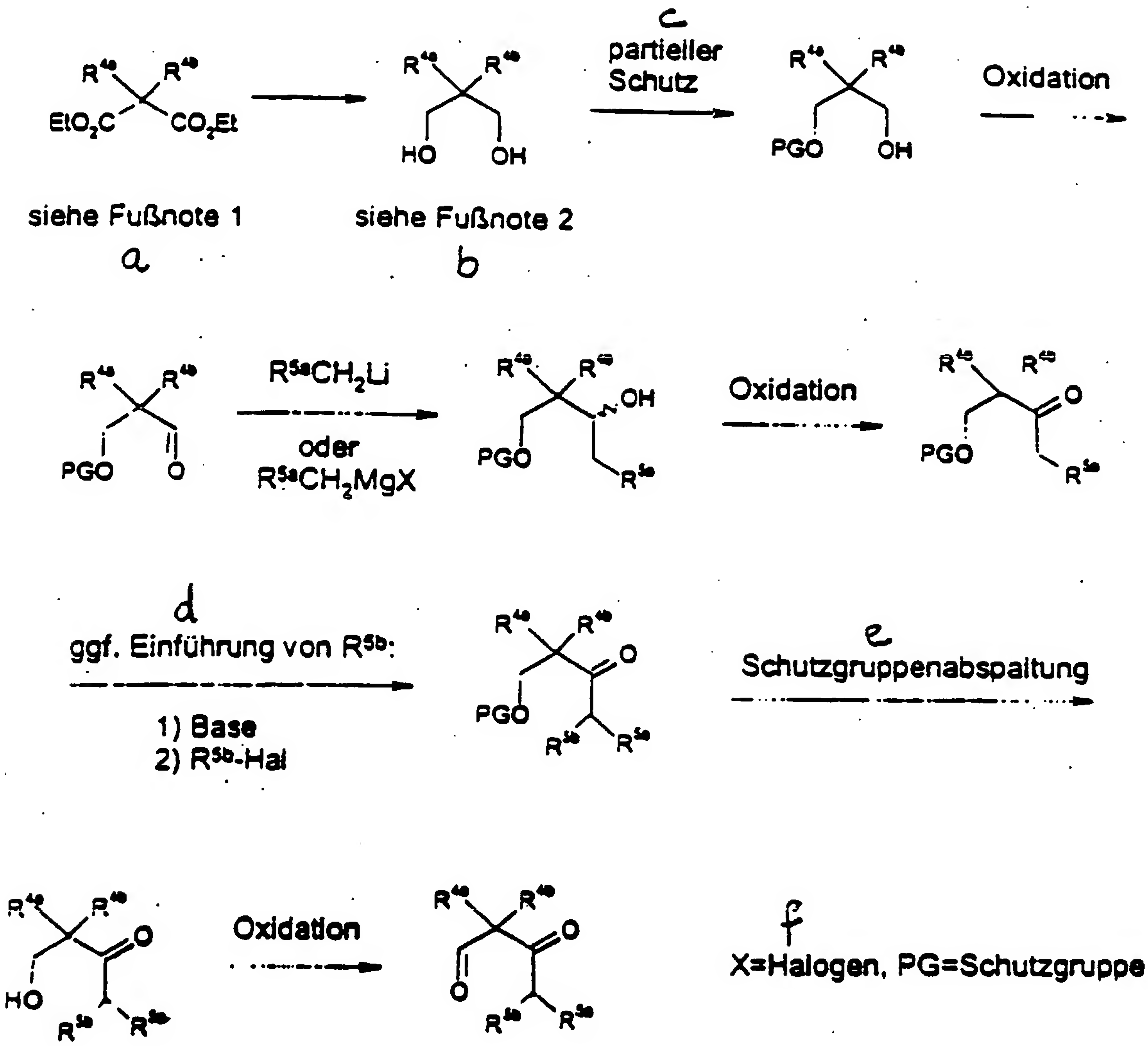
Later, the stereochemistry of the hydroxyl group in position 3 will be controlled by the selection of the chiral auxiliary.

The compounds necessary for the method according to the invention with general formula III are available commercially or can be prepared in a simple manner.

If the compounds of general formula III are not commercially available, they can be prepared, for example, according to the methods given in Figure 1 and Figure 2.

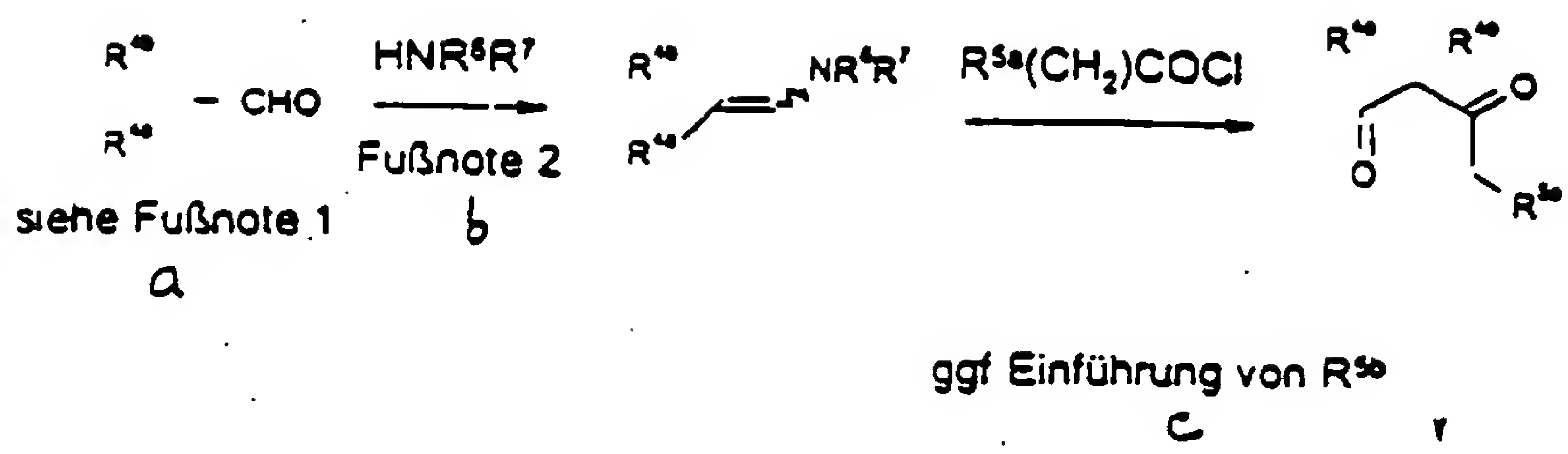
Figure 1. The starting material is (substituted) malonic acid ester

Key to the Figure:
a - see footnote 1
b - see footnote 2
c - partial protection
d - optional introduction of R^{5b}
e - cleavage of the protective group
f - X = halogen, PG = protective group
general: oder = or



1) See starting material C, where R^{4a} + R^{4b} = trimethylene.
2) These 1,3-propanediols are partly available commercially and then can be used at this point in the synthesis.

Figure 2.
Key:
a - see footnote 1
b - footnote 2
c - optional introduction of R^{5b}



1) These starting materials are commercially available or can be obtained by methods known to the expert.
2) Secondary amine: preferably piperidine or morpholine or R^6 and R^7 independently of one another stand for a straight-chain or branched C_1-C_6 alkyl group.

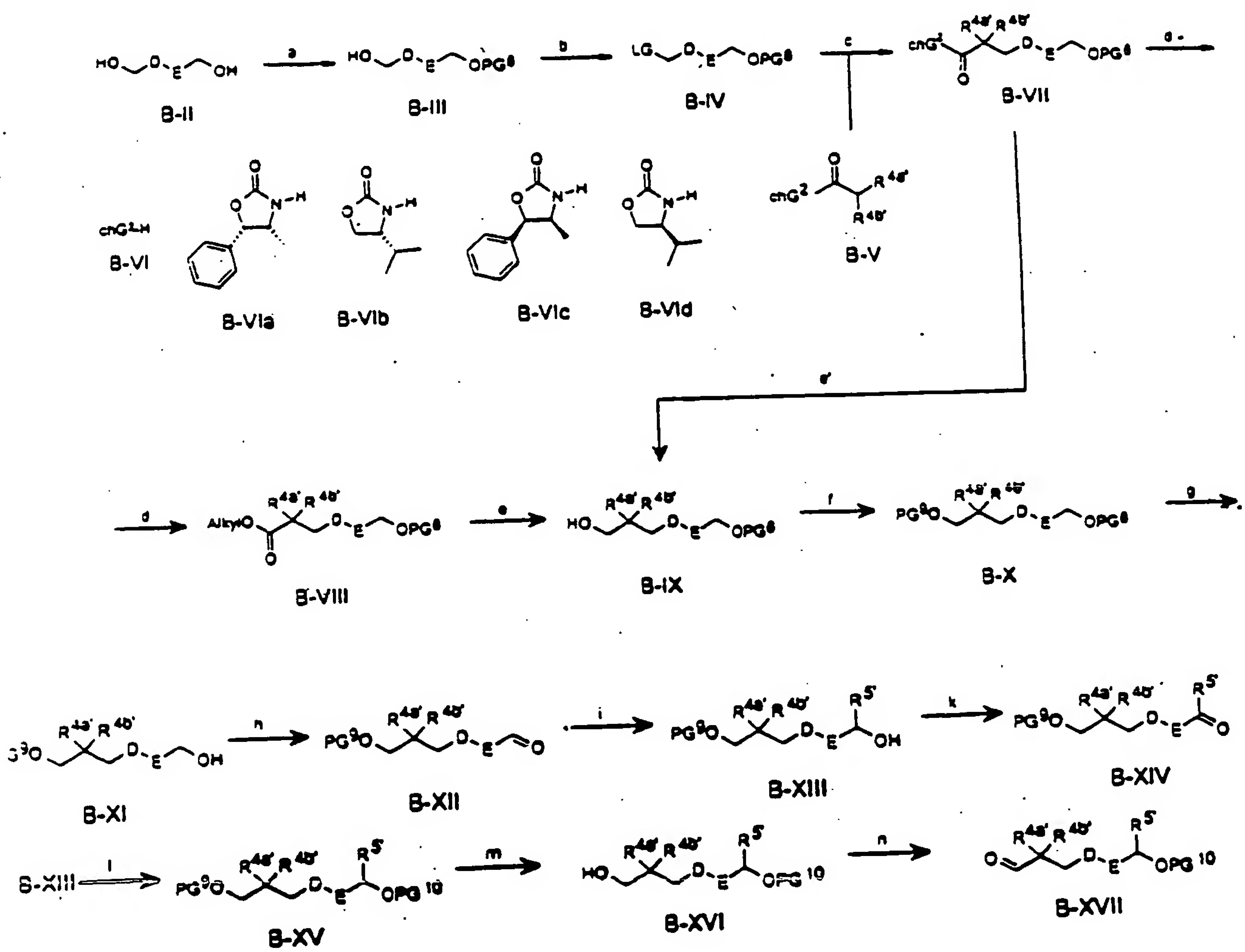
The building blocks having general formula I, prepared according to the present invention, can be used according to the methods described, for example, following from page 2 of this Application text (Schinzer et al.: Chem. Eur. J. 1996, 2, No. 11, 1477-1482; Angew. Chem. 1997, 109, No. 5, p. 543-544; Nicolaou et al.: Angew. Chem. 1997, 109, No. 1/2, p. 170-172; Nature, Vol. 387, 1997, p. 268-272; J. Am. Chem. Soc., Vol. 119, No. 34, 1997, p. 7960-7973; J. Am. Chem. Soc., Vol. 119, No. 34, 1997, p. 7974-7991; Angew. Chem. 1997, 109, No. 19, p. 2181-2187) for the synthesis of epothilone A and B as well as for epothilone derivatives correspondingly modified in the C_1-C_6 section of the epothilone skeleton.

Thus, with the compounds having general formula A", the variability of the substituents demanded at the outset is achieved.
A great advantage of the method according to the invention also lies in the fact that the chiral auxiliary (4R,5S)- or (4S,5R)-4-methyl-5-phenyl-2-oxazolidinone used can be recovered easily after cleavage from the protected compound having general formula IV and can be used again without any loss of optical induction in the synthesis.
The building blocks obtained in these ways, also their enantiomers or mixtures of these enantiomers, are suitable for the aldo [sic, aldol?] condensation with an epothilone building block, which carries a carbonyl function on C-7 (epothilone numbering) as is the case in the total syntheses of epothilone A and epothilone B given above.

The building blocks A, their enantiomers or mixtures of these enantiomers are thus suitable for esterification with an epothilone building block which carries a hydroxyl function on C-15 (epothilone numbering) as is the case in the total syntheses of epothilone A and B.

Preparation for the partial fragments B:

Scheme 4



Step a (BII → B-III):

A hydroxyl group in B-II is protected according to methods known to the expert. As protective group PG^8, those protective groups known to the expert come into consideration as they were already named before for PG^4 in Step a) (A-II → A-III).

Preferred are silicon-containing protective groups, which can be cleaved off under acidic reaction conditions or using fluoride, for example, the trimethylsilyl, triethylsilyl, tert.-butyldimethylsilyl, tert.-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl groups.
The tert.-butyldimethylsilyl group is especially preferred.

Step b (B-III → B-IV):
The free hydroxyl group in B-III is converted into the leaving group LG according to methods known to the expert. For example, halogens, such as bromine or iodine or alkyl- or arylsulfonates, which are prepared from the corresponding sulfonic acid halides or sulfonic acid anhydrides according to methods known to the expert, are suitable as the leaving group LG.
The preferred leaving group LG is trifluoromethanesulfonate.

Step c (B-IV → B-VII):
The compound B-IV is alkylated with the enolate of a carbonyl compound having general formula B-V, where chG^2 is a simple alkoxy group but it can also be a chiral auxiliary group, using methods known to the expert. The enolate is prepared by the action of strong bases, for example, lithium diisopropylamide, lithium hexamethyldisilazane, at low temperatures. Chiral alcohols, which can be prepared in the optically pure form and are inexpensive, for example, pulegol, 2-phenylcyclohexanol, 2-hydroxy-1,2,2-triphenylethanol, 8-phenylmenthol or compounds containing reactive NH groups which can be prepared in the optically pure form and are inexpensive, for example, amines, amino acids, lactams or oxazolidinones, are suitable as chiral auxiliary group chG^2-H (B-VI). Oxazolidinones are preferred, especially the compounds having formulas B-VIa to B-VId. By the choice of the particular antipodes, the absolute stereochemistry on the α-carbonyl carbon of the compound having general formula B-VII is established. In this way, one can obtain compounds having general formulas B-VII to B-XVII or their respective enantiomers ent-B-VII to ent-B-XVII. If an achiral alcohol, for example, ethanol, is used as chG^2-H (B-VI), one obtains the racemic compounds rac-B-VII to rac-B-XVII.

Step d (B-VII → B-VIII):
If the group chG^2 represents one of the chiral groups mentioned in Step c), then this is recovered by transesterification of B-VII into an alkyl ester having the general formula B-

VIII. The transesterification is carried out according to methods known to the expert. Transesterification with simple alcohols, for example, methanol or ethanol, in the presence of the corresponding titanium(IV) alcoholates is preferred.

Step e (B-VIII → B-IX):

The ester in B-VIII is reduced to the alcohol B-IX. Reducing agents known to the expert are suitable as reducing agents, for example, aluminum hydrides, for example, lithiumaluminum hydride or diisobutylaluminum hydride. The reaction is carried out in an inert solvent, for example, diethyl ether, tetrahydrofuran, toluene.

Step e' (B-VII → B-IX):

Alternatively to Steps d) and e), the carbonyl group in B-VII can be reduced directly to the alcohols having general formula B-IX under the conditions described in Step e). Here, again, the chiral auxiliary component chG^2-H can be recovered.

Step f (B-IX → B-X):

The free hydroxyl group in B-IX is protected according to methods known to the expert. As protective groups PG^9, the protective groups known to the expert come into consideration, as they were already named for PG^4 in Step a) (A-II → A-III).

Those protective groups are preferred which can be cleaved under acidic reaction conditions, for example, the methoxymethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl groups. The tetrahydropyranyl group is especially preferred.

Step g (B-X → B-XI):

The protective group PG^8 introduced in Step a) is now cleaved according to methods known to the expert. If this is a silyl ether, then reaction with fluorides, for example, tetrabutylammonium fluoride, the hydrogen-fluoride-pyridine complex, potassium fluoride or the use of dilute mineral acids, the use of catalytic amounts of acids, for example, para-toluenesulfonic acid, para-toluenesulfonic acid pyridinium salt, camphorsulfonic acid in alcoholic solutions, for example, in ethanol or isopropanol are suitable for the cleavage.

Step h (B-XI → B-XII):

The oxidation of the primary alcohol in B-XI to the aldehyde in general formula B-XII is done according to methods known to the expert. For example, one can mention the oxidation with pyridinium chlorochromate, pyridinium dichromate, chromium trioxide-pyridine complex, the oxidation according to Swern or related methods, for example, with the use of oxalyl chloride in dimethylsulfoxide, the use of the Dess-Martin periodinan, the use of nitrogen oxides, for example, N-methylmorpholino-N-oxide in the presence of suitable catalysts, for example, tetrapropylammonium perruthenate in inert solvents. Oxidation according to Swern as well as with N-methylmorpholino-N-oxide using tetrapropylammonium perruthenate are suitable.

Step i (B-XII → B-XIII):

The reaction of the aldehyde B-XII to alcohols having general formula B-XIII is done according to methods known to the expert with organometallic compounds having the general formula M-$R^{5'}$, where M stands for an alkali metal, preferably lithium or a divalent metal MX, where X is a halogen and the group $R^{5'}$ has the meaning given above. Preferably, magnesium and zinc are used as divalent metal and the halogen X is preferably chlorine, bromine or iodine.

Step k (B-XIII → B-XIV):

The oxidation of the alcohol B-XIII to the ketone in general formula B-XIV is done as in h) according to known methods. Oxidation with N-methylmorpholino-N-oxide using tetrapropylammonium perruthenate is preferred.

Step l (B-XIII → B-XV):

The hydroxyl group in B-XIII can be provided with a protective group PG^{10} according to the methods given in a). Silicon-containing protective groups, which can be cleaved off under acidic reaction or using fluoride are preferred, for example, trimethylsilyl, triethylsilyl, tert.-butyldimethylsilyl, tert.-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl groups. The tert.-butyldiphenylsilyl group is especially preferred.

Step m (B-XV → B-XVI):

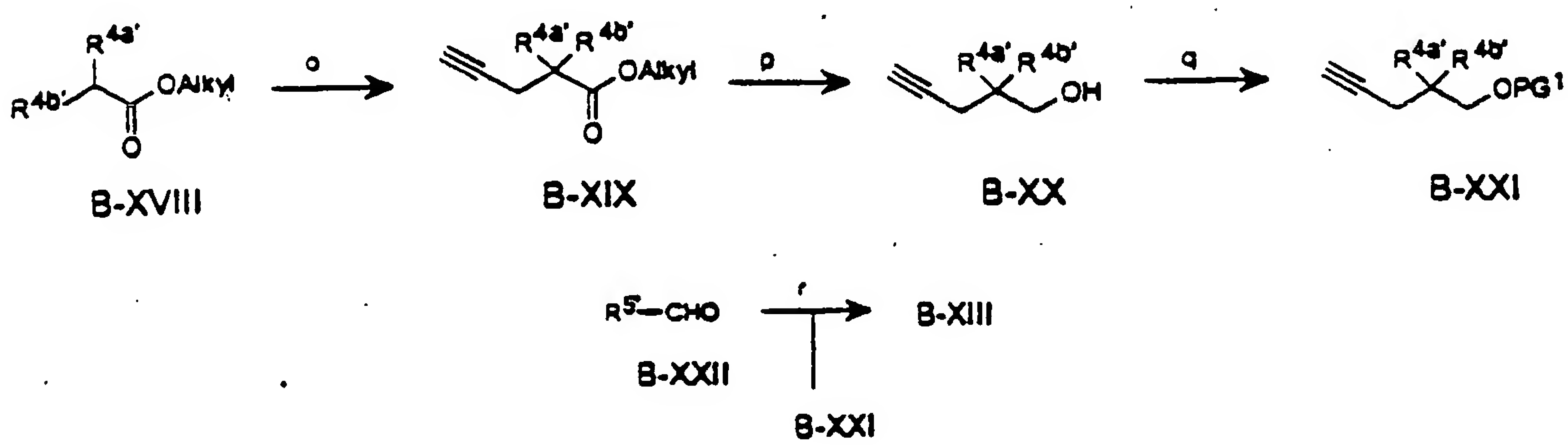
The protective group PG^9 introduced in Step f) is cleaved off according to the method described in Step g).

Step n (B-XVI → B-XVII):

The oxidation of the alcohol B-XVI into the aldehyde having general formula B-XVII is done according to the methods given in h). Oxidation according to Swern is preferred.

Alternatively, the compounds having general formula B-XIII can be prepared according to the route described in Scheme 5.

Scheme 5



Step o (B-XVIII → B-XIX):

Starting from the inexpensively obtainable acetic ester derivatives having general formula B-XVIII, in which $R^{4a'}$ and $R^{4b'}$ have the meanings given above, the ester enolate is prepared by the action of strong bases, for example, lithium diisopropylamide, lithium hexamethyldisilazane at low temperatures and are reacted with 3-halogeno-1-propine, preferably 3-bromo-1-propine to compounds having the general formula B-XIX.

Step p (B-XIX → B-XX):

The reduction of the ester B-XIX to the alcohol B-XX is done according to the methods described in Step e), preferably using diisobutylaluminum hydride.

Step q (B-XX → B-XXI):

The hydroxyl group in B-XX can be provided with a protective group PG^{11} under the conditions given under a). Preferably, silicon-containing protective groups are used which can be cleaved off under acidic reaction conditions or using fluoride, for example, the trimethylsilyl, triethylsilyl, tert.-butyldimethylsilyl, tert.-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl groups.

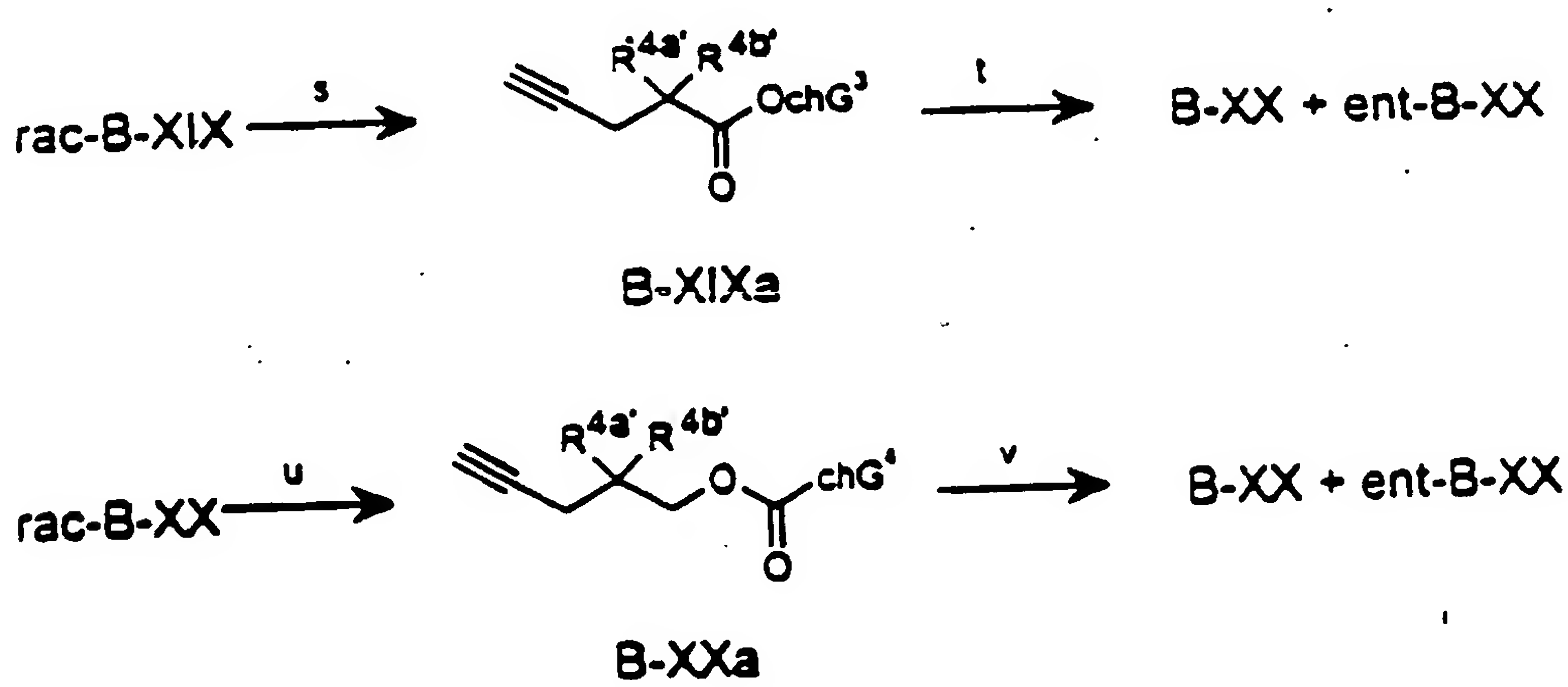
The tert.-butyldimethylsilyl group is especially preferred.

Step r (B-XXI → B-XIII):

The acetylene B-XXI can be deprotonated according to methods known to the expert and the obtained acetylide can be reacted with carbonyl compounds having general formula B-XXII, in which $R^{5'}$ has the meaning given above, to form an alcohol having general formula XIII. Alkyl alkali compounds are suitable for deprotonation, for example, butyl lithium or other strong bases, for example, alkylhexamethyldisilazane or lithium diisopropylamide. n-Butyl lithium is preferred.

Using the route described in Scheme 5, first the racemic compounds rac-B-XIII are obtained. Optionally, the steps rac-B-XIX and rac-B-XX according to Scheme 6 provide the possibility of chemical resolution of the racemate and thus also an access to the pure enantiomeric compounds B-XX or ent-B-XX, as long as $R^{4a'}$ is not identical with $R^{4b'}$.

Scheme 6



Step s (rac-B-XIX → B-XIXa):

The racemic compound rac-B-XIX can be transesterified with a chiral alcohol which can be obtained in the optically pure form chG^3-OH using methods known to the expert, for example, using the method given under Step d) to form a mixture of diastereomeric esters B-XIXa and separate these with simple chromatographic methods. For example, pulegol, 2-phenylcyclohexanol, 2-hydroxy-1,2,2-triphenylethanol, 8-phenylmenthol come into consideration as chiral alcohols.

Step t (B-XIXa → B-XX and ent-B-XX):

The diasteromerically pure esters B-XIXa can be reduced according to the method given under Step e) to the alcohols B-XX and ent-B-XX, where the auxiliary component chG^3-OH described in Step s) can be recovered.

Step u (rac-B-XX → B-XXa):

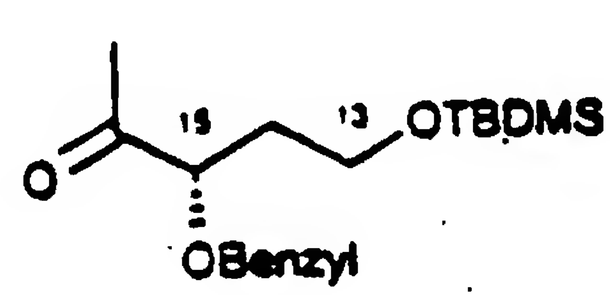
The racemic compound rac-B-XX can be reacted with a chiral acid chG^4-CO_2H, obtainable in the optically pure form, its ester anhydride or acid halide according to the methods known to the expert to form a mixture of the diastereomeric esters XXa and can be separated with simple chromatographic methods. For example, malic acid, tartaric acid or their derivatives come into consideration as chiral acids.

Step v (B-XXa → B-XX and ent-B-XX):

The diastereomerically pure esters B-XXa can be reduced according to the methods given under Step e) to the alcohols B-XX or ent-B-XX, or saponified according to methods known to the expert, where, in the latter case, the auxiliary component described under Step u), chG^4-CH_2H, can be recovered.

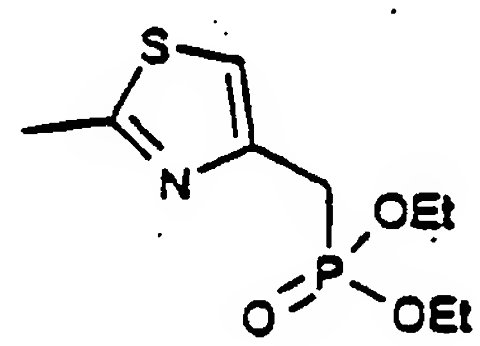
Preparation of partial fragments C:

It is known that the compound having the formula

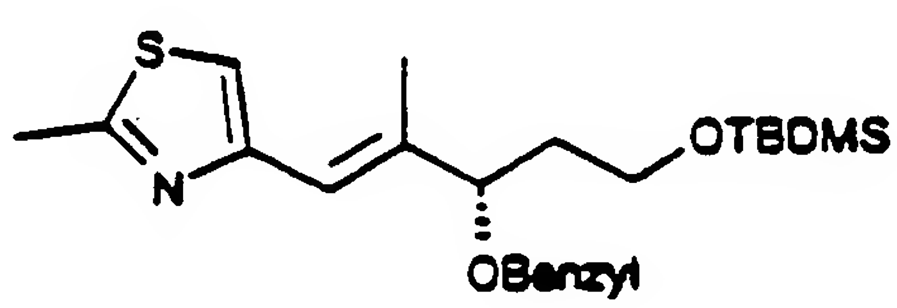


(TBDMS stands for a tert.-butyldimethylsilyl group) can be used for the synthesis of the C13-C16 fragments (epothilone numbering) of epothilone A (Schinzer et al., Chem. Eur. J. 1996, 2, No. 11, 1477-1482). The synthesis described by Schinzer et al. leads to the necessary chirality through kinetic resolution of the racemate according to Sharpless. A necessary chromatographic separation, insufficient excess of the enantiomer (80% ee) and a low total yield disqualify this route for industrial synthesis, which requires high yields and high optical purity.

Furthermore, it is known that the synthesis building block named above can be converted with the phosphonate having the formula



by a Wittig reaction into a compound having the formula

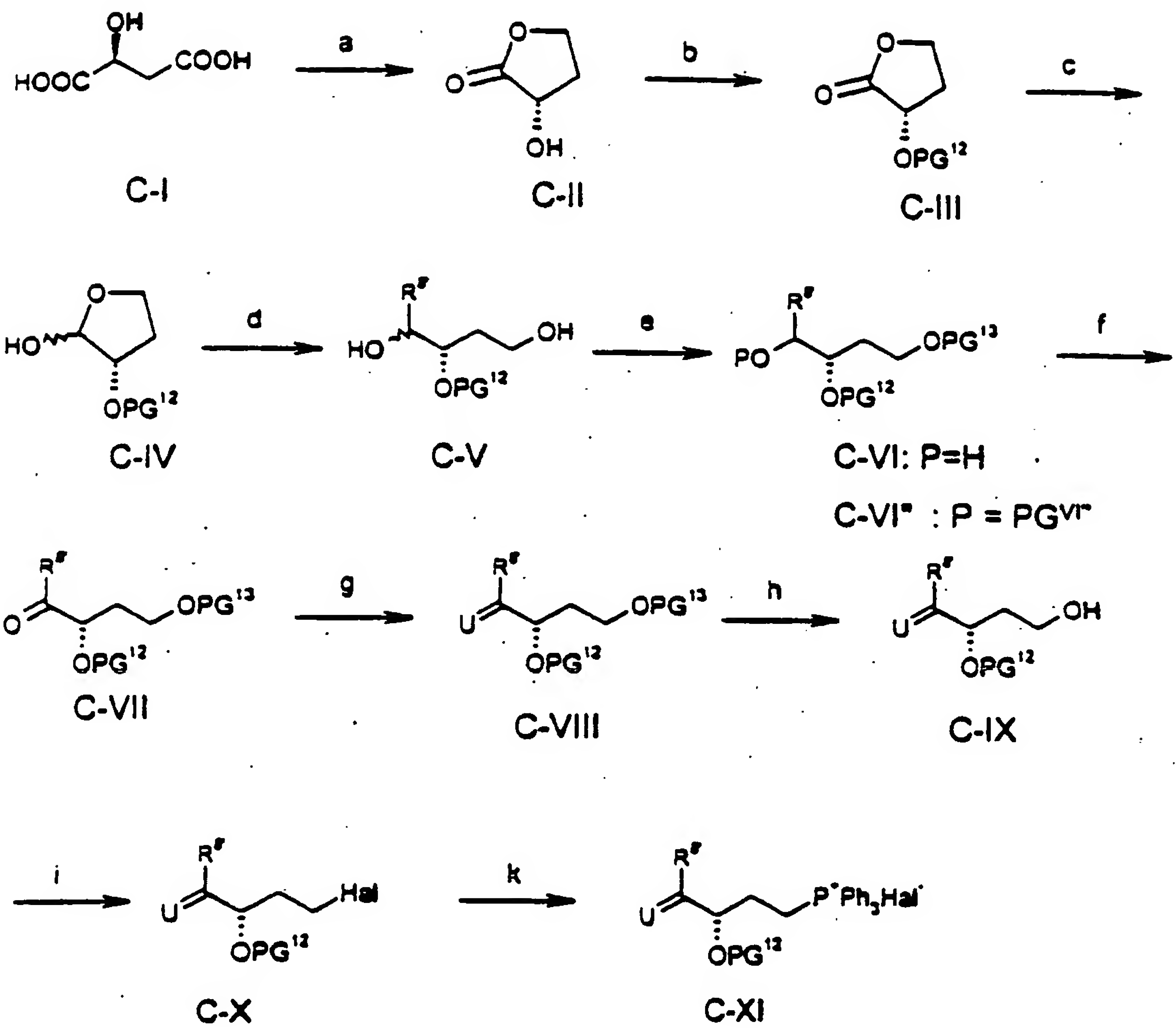


which then can be used for the introduction of the C13-C20 fragment for the epothilone synthesis.

Partial fragments of the formula C can be prepared from cheap, inexpensively accessible malic acid in an efficient way with high optical purity (>99.5%ee).

The synthesis is described in the following Scheme 7 on the example of L-(-)-malic acid (C-1). Starting from D(+)-malic acid (ent-C-1), one obtains the corresponding enantiomeric compounds (ent-C-II to ent-C-XI) and starting from racemic malic acid (rac-C-1), the corresponding racemic compounds (rac-C-II to rac-C-XI) can be obtained.

Scheme 7



Step a (malic acid C-1 → C-II):
L-(-)-malic acid is converted into the hydroxylactone C-II according to a method known in the literature (Liebigs Ann. Chem. 1993, 1273-1278).

Step b (C-II → C-III):
The free hydroxyl group is protected in compound C-II according to methods known to the expert. As protective group PG^{12}, the protective groups known to the expert come into consideration as they were already named above for PG^4 in Step a) (A-II → A-III]). Those protective groups are preferred, which can be cleaved under the action of fluoride, but are

stable under weakly acidic reaction conditions, for example, the tert.-butyldiphenylsilyl, tert.-butyldimethylsilyl, or triisopropylsilyl groups are especially preferred.

Step c (C-III → C-IV):
The lactone C-III is reduced to the lactol C-IV according to methods known to the expert. Aluminum hydrides, modified in their reactivity, for example, diisobutylaluminum hydride, are suitable as reducing agents. The reaction is carried out in an inert solvent, for example, toluene, preferably at low temperatures (-20 to -100°C).

Step d (C-IV → C-V):
The reaction of the lactol C-IV to compounds having formula C-V is done with organometallic compounds having the general formula M-$R^{8'}$, where M stands for an alkali metal, preferably lithium, or a divalent metal MX, where X represents a halogen and $R^{8'}$ has the meanings given above. Magnesium and zinc are preferred as divalent metal and the halogen X is preferably chlorine, bromine and iodine.

Step e (C-V → C-VI):
The primary hydroxyl group in compound C-V is protected selectively with respect to the secondary hydroxyl group according to methods known to the expert. The secondary hydroxyl group is optionally then also protected using methods commonly known by the expert.
As protective groups PG^{13} and $PG^{VI'}$, those protective groups known to the expert that come into consideration, which were already named before for PG^4 in Step a) (A-II → A-III). Those protective groups are preferred which can be cleaved selectively under weakly acidic conditions in the presence of the protective group PG10, which is introduced from building block A in the synthesis of the compound having general formula I, for example, trimethylsilyl, triethylsilyl, tert.-butyldimethylsilyl groups.
The tert.-butyldimethylsilyl group is especially preferred.

Step f (C-VI → C-VII):
The oxidation of the secondary alcohol in C-VI to the ketone C-VII is done according to methods known to the expert. For example, let us mention the oxidation with pyridinium chlorochromate, pyridinium dichromate, chromium trioxide-pyridine complex, the oxidation

according to Swern or related methods, for example, using oxalyl chloride in dimethylsulfoxide, using the Dess-Martin periodinan, the use of nitrogen oxides such as N-methylmorpholino-N-oxide in the presence of suitable catalysts, such as, for example, tetrapropylammonium perruthenate in inert solvents. The oxidation according to Swern is preferred.

Step g (C-VII → C-VIII):

For compounds in which U is equal to CR10'R11', this group is established according to methods known to the expert. For this purpose, methods such as, for example, the Wittig- or Wittig-Horner reaction, the addition of an organometallic compound MCHR10'R11' with the cleavage of water are suitable. The Wittig- and Wittig-Horner reaction using phosphonium halides of the type $CR10'R11'P(Ph)3^{+}Hal^{-}$ or phosphonates of the type CR10'R11'P(O)-$(Oalkyl)_2$ with Ph being equal to phenyl, R10', R11' and halogen in the meanings given with strong bases such as, for example, n-butyllithium, potassium-tert.-butanolate, sodium methanolate, sodium hexamethyldisilazane is preferred. n-Butyllithium is preferred as the base.

For compounds in which U represents two alkoxy groups OR^{23} or a C_2-C_{10} alkylene-α,ω-dioxy group, the ketone is ketalized according to methods known to the expert, for example, using an alcohol HOR^{23} or a C_2-C_{10} alkylene-α,ω-diol under acid catalysis.

Step h (C-VIII → C-IX):

The protective group PG^{13} introduced under e) is now cleaved selectively according to methods known to the expert in the presence of PG^{12}. If this is a protective group that can be cleaved with an acid, the cleavage is preferably carried out under weakly acidic conditions, for example, by reaction with dilute organic acids in inert solvents. Acetic acid is preferred.

Step i (C-IX → C-X):

Optionally, the free primary hydroxyl group is converted into a halide according to methods known to the expert. Preferred halides are chlorine, but especially bromine and iodine. The substitution of the hydroxyl group for a bromine atom can be carried out, for example, with triphenylphosphine/tetrabromomethane, but also according to any other method known to the expert. The establishment of an iodine atom can be achieved from the bromide by substitution, for example, with sodium iodide in acetone according to Finkelstein.

The direct conversion on the hydroxyl group into the iodide is also possible, for example, using elemental iodine, imidazole and triphenylphosphine in dichloromethane.
Finally, if U should stand for H/OR^9 with R^9 meaning a hydrogen atom, the conversion of the primary hydroxyl group into a halogen atom is carried out in the stage of compound C-VI' after selective deprotection of the primary hydroxyl group.

Step k (C-X → C-XI):
If the linking of the C13-C16 unit with position 12 of the epothilone group or epothilone fragments, for example, in C7-C12 unit by the Wittig reaction, for example, as described in Nature, Volume 387, 268-272 (1997), then starting from the halides C-X, the triphenylphosphonium halides (R^{21} = $P(Ph)_3{}^+Hal^-$), alkyl or arylphosphonates (R^{21} = $P(O)(OQ)_2$) or phosphine oxides (R^{21} = $P(O)Ph_2$) of type C-XI are prepared according to methods known to the expert. In this case, Ph stands for phenyl; Hal stands for F, Cl, Br or I and Q is a C_1-C_{10} alkyl or phenyl group.
For the preparation of the phosphonium salts, for example, the reaction of the corresponding halides with triphenylphosphine is suitable in solvents, such as toluene or benzene.
The preparation of the phosphonates can be carried out, for example, by reaction of the halides C-X with a metallized dialkyl phosphite. The metallization is usually done with strong bases, such as butyllithium.
The preparation of the phosphine oxides can be carried, for example, by reaction of the halides C-X with metallized diphenylphosphine and subsequent oxidation. Again, strong bases such as butyllithium are suitable for the metallization. The subsequent oxidation to the phosphine oxide can be carried out then, for example, with dilute aqueous hydrogen peroxide solution.

It was found that compounds having the formula C' can be prepared from the inexpensively obtainable pure enantiomeric malic acid in a surprisingly efficient way with high optical purity (> 99.5% ee), although, in principle, in the described method according to the invention, the possibility of complete or partial racemization would exist.
As mentioned at the outset, the known method yields those compounds in which R^1 is a methyl group, R^2 is a tert.-butyldimethylsilyl or benzyl group, R^3 is an O-tert.-butyldimethylsilyl group and X is an oxygen atom or a (2-methylthiazol-4-yl)methylene group, only in an optical purity of approximately 80%ee.

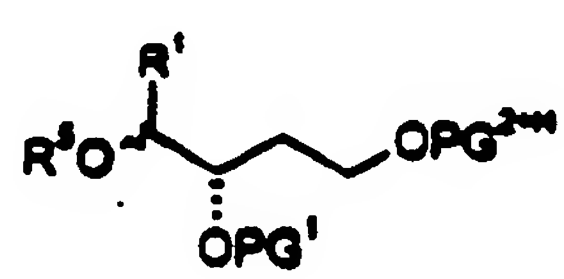
In addition, the chemical yields of the method according to the invention are significantly higher than the yields given in the method described by Schinzer et al. For example, the yield of the (3S)-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-pentanone starting from L-(-)-malic acid prepared according to the method of the invention is almost twice as high, 26.5%, as that given by Schinzer et al., for the preparation of (3S)-3-benzyloxy-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2-pentanone (14.35%; Chem. Eur. J. 1996, 2, No. 11, 1477-1482) or the yield achieved in the preparation of (3S)-3-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2-pentanone (20.58%; Angew. Chem. 1997, 109, No. 5, 543-544).
This comparison is based on the yields given in the quoted references where - as already mentioned above - it must be taken into consideration that the compounds obtained according to the known methods are not obtained in the pure enantiomeric form, so that the actual yield of the respective enantiomerically pure compound is lower and a further purification step at this or at a later stage in the process will become necessary in order to obtain the compound in the pure enantiomeric form.

Moreover, the method according to the invention makes it possible to have a very broad variation of the substituents in this C13-C16 building block.

Thus, the present invention is concerned with a method for the preparation of compounds having general formula C', which is characterized by the fact that
L-(-)-malic acid, D-(+)-malic acid or racemic malic acid is used as starting material.

Preferably, optically pure D-(+)- or L-(-)-malic acid is used.

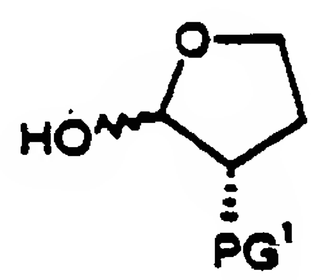
The invention is also concerned with the intermediate compounds of general formula V, VI and VI' that occur in the process (summarized below as VI")



VI"

where
R^1, PG^1 and R^5 have the meaning given in general formula C' and
PG^{2+H} stands for a hydrogen atom or a protective group PG^2.

These compounds are prepared according to the invention by adding to a compound having general formula IV



IV

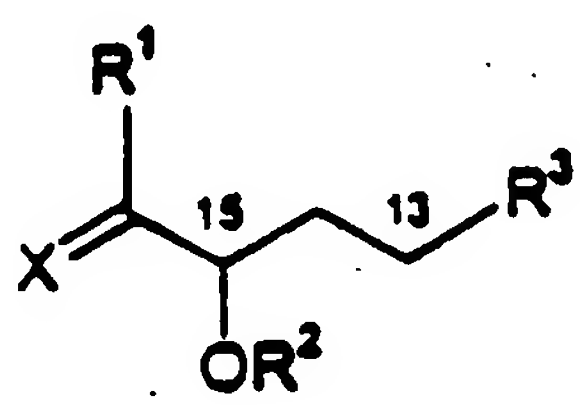
where
PG^1 has the meaning given in general formula C,
with opening of the lactol ring, an organometallic compound having general formula

$$R^1Y$$

where R^1 has the meaning given in general formula C' and
Y stands for an alkali metal atom or MZ, where M is a divalent metal atom and Z is a halogen atom.

Lithium is preferred as alkali atom.
In the case of MZ, magnesium and zinc are preferred for the divalent metal atom; namely chlorine, bromine and iodine come into consideration as halogen atom.

Moreover, the present invention is concerned with the new C13-C16 epothilone building blocks having general formula C



C,

where

R^1 stands for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl, which all can be substituted,

R^2 stands for hydrogen or a protective group PG^1,

R^3 stands for a hydroxyl group, halogen, a protected hydroxyl group OPG^2, a phosphonium halide group $PPh_3^+Hal^-$ (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate group $P(O)(OQ)_2$ (Q = C_1-C_{10} alkyl or phenyl) or for a phosphine oxide group $P(O)Ph_2$ (Ph = phenyl),

X stands for an oxygen atom, two alkoxy groups OR^4, a C_2-C_{10} alkylene-α,ω-dioxy group, which may be straight-chain or branched, H/OR^5 or a group CR^6R^7,

where

R^4 stands for a C_1-C_{20} alkyl group,

R^5 stands for hydrogen or a protective group PG^3,

R^6, R^7 are the same or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl group or R^6 and R^7 together with the methylene carbon atom stand for a 5- to 7-membered carbocyclic ring,

where not at the same time

R^1 can be a methyl group, R^2 can be a tert.-butyldimethylsilyl- or benzyl group, R^3 can be an O-tert.-butyldimethylsilyl group and X can be a (2-methylthiazol-4-yl)methylene group or

R^1 can be a methyl group, R^2 can be a tert.-butyldimethylsilyl group, R^3 can be a triphenylphosphonium iodide group and X can be a (2-methylthiazol-4-yl)methylene group.

With the first disclaimer, those compounds are excepted which were already prepared by Schinzer et al. according to a method other than the method according to the invention (Chem. Eur. J. 1996, 2, No. 11, 1477-1482 and Angew. Chem. 1997, 109, No. 5, 543-544).

The second disclaimer considers the (5E,3S)-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-yl]-triphenylphosphonium iodide, mentioned by K. C. Nicolaou et al. in Nature, Volume 387, 1997, 268-272.

For more detailed explanation of the substituents R^1, R^4, R^6, R^7, PG^1, PG^2 and PG^3 that occur in general formula C, the statements made before regarding the substituents of general formula C' apply.

According to the invention, those compounds having general formula C are preferred, wherein

R^1 stands for a hydrogen atom, an optionally substituted C_1-C_4 alkyl group, an optionally free hydroxyl group or protected hydroxyl group OPG^4, optionally substituted with 1 to 3 groups selected from the group of halogen substituents, C_1-C_4 alkyl, azido, nitro, nitrile and amino (NH_2), substituted phenyl group, and/or

X stands for an oxygen atom and/or

the aryl group that stands for R^6 and/or R^7 stand for an aryl group optionally substituted with 1 to 3 groups, selected from the group of substituents of halogen, free hydroxyl group or protected hydroxyl group OPG^5, CO_2H, CO_2 alkyl, C_1-C_4 alkyl, azido, nitro, nitrile, amino (NH_2), substituted phenyl group or for a 5- or 6-membered heteroaryl group, optionally substituted with C_1-C_4 alkyl groups,
especially for a substituent selected from the group 2-, 3-furanyl-, 2-, 3-, 4-pyridinyl-, 2-, 4-5-thiazolyl-, 2-, 4- and 5-imidazolyl group, which is optionally substituted by 1 or 2 C_1-C_4 alkyl groups and/or

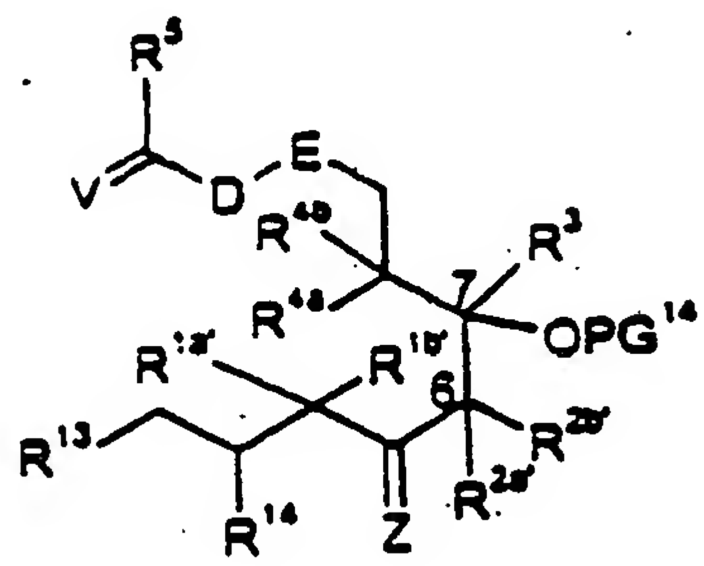
PG^1, PG^2 and PG^3 are selected from the group of substituents methoxymethyl-, methoxyethyl-, ethoxyethyl-, tetrahydropyranyl-, tetrahydrofuranyl-, trimethylsilyl-, triethylsilyl-, tert.-butyldimethylsilyl-, tert.-butyldiphenylsilyl-, tribenzylsilyl-, triisopropylsilyl-, benzyl-, para-nitrobenzyl-, para-methoxybenzyl-, acetyl-, propionyl-, butyryl- and benzoyl group, especially PG^1 is a tert.-butyldiphenylsilyl-, tert.-butyldimethylsilyl-, or triisopropylsilyl group, and

especially PG^2 is a tert.-butyldimethylsilyl-, acetyl-, benzoyl-, benzyl-, tetrahydropyranyl group.

All of the protective groups given for PG^1, PG^2 and PG^3 come into consideration as protective groups PG^4 and PG^5.

Preparation of the partial fragments ABC and their cyclization to I:

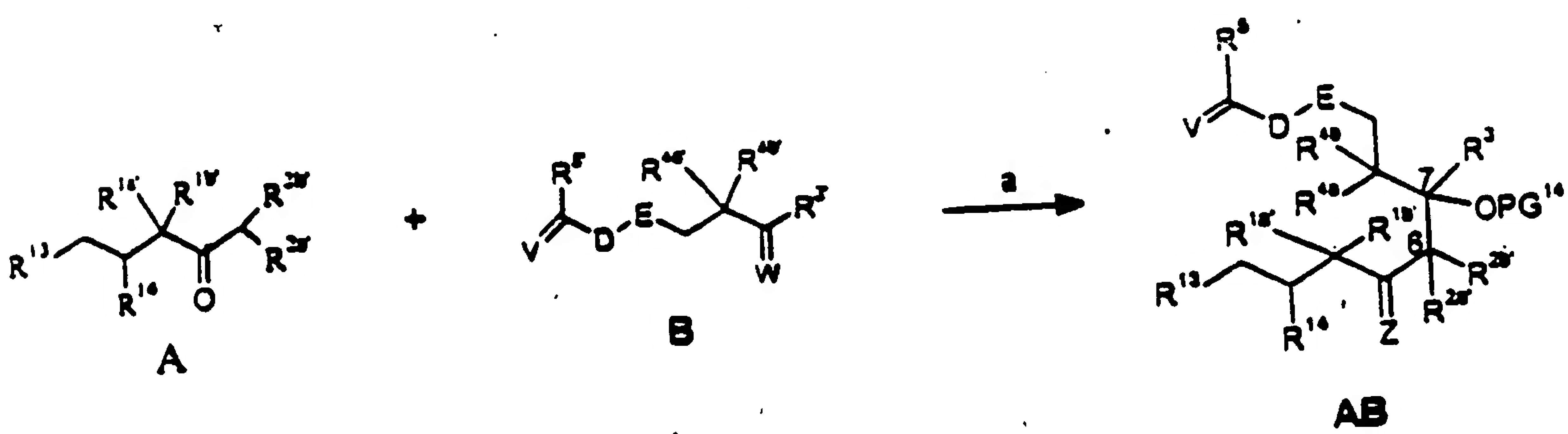
Partial fragments having general formula AB



AB,

where $R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, R^3, R^{4a}, R^{4b}, R^5, R^{13}, R^{14}, D, E, V and Z have the meanings already given above and PG^{14} stands for a hydrogen atom or a protective group PG, are obtained from the previously described fragments A and B according to the method shown in Scheme 8.

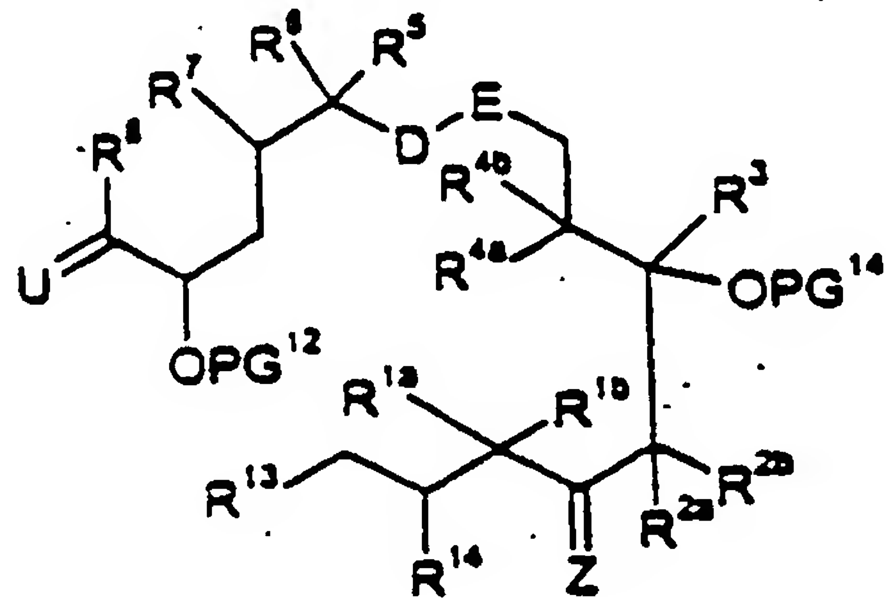
Scheme 8



Step a (A + B → AB):

The compound B, where W has the meaning of an oxygen atom and is protected optionally by additional carbonyl groups, is alkylated with the enolate of a carbonyl compound having the general formula A. The enolate is prepared by the action of strong bases, for example, lithium diisopropylamide, lithium hexamethyldisilazane at low temperatures.

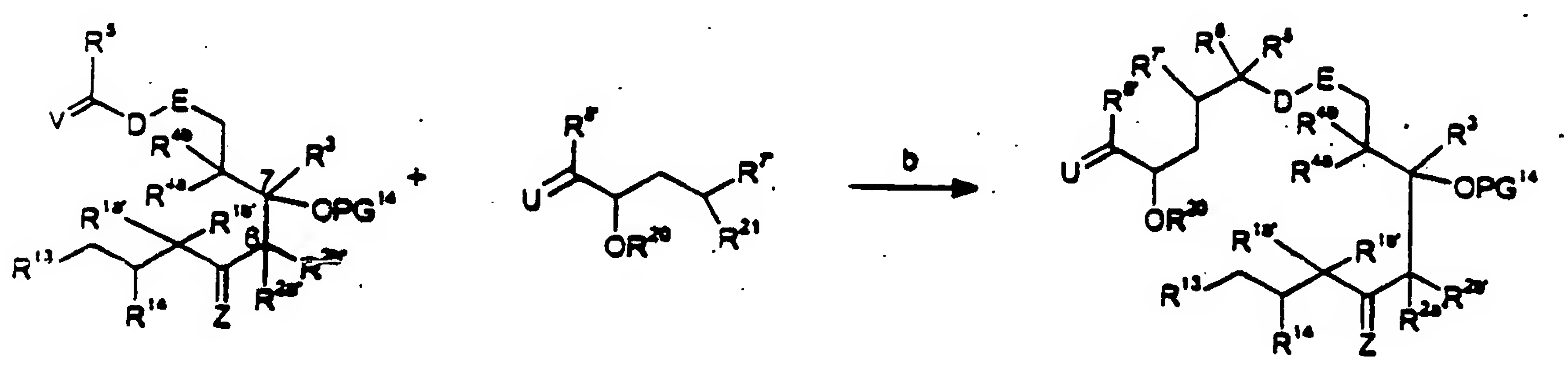
Partial fragments of general formula ABC



ABC,

where $R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, R^3, R^{4a}, R^{4b}, R^5, R^6, R^7, R^8, R^{13}, R^{14}, D, E, U and Z have the meanings already given above, are obtained from the previously described fragments AB and C according to the method shown in Scheme 9.

Scheme 9



Step b (AB + C → ABC):

The compound C, in which R^{21} has the meaning of a Wittig salt and is protected optionally by additional carbonyl groups, is deprotonated with a suitable base, for example, n-butyllith-

ium, lithium diisopropylamide, potassium-tert.-butanolate, sodium- or lithium hexamethyl-disilazide and is reacted with a compound AB, where V has the meaning of a hydrogen atom.

Step c (ABC → I):

The compounds ABC, in which R^{13} is a carboxylic acid CO_2H and R^{20} represents a hydrogen atom, is reacted according to methods known to the expert for the formation of larger macrolids to form compounds having formula I, in which Y has the meaning of a hydrogen atom. Preferably, the method described in "Reagents for Organic Synthesis, Volume 16, p. 353" using 2,4,6-trichlorobenzoic acid chloride and suitable bases, such as triethylamine, 4-dimethylaminopyridine, sodium hydride is used.

Step d (ABC → I):

The compounds ABC, in which R^{13} is a CH_2OH group and R^{20} is a hydrogen atom, can be reacted preferably by using triphenylphosphine and azo diesters, for example azodicarboxylic acid diethyl ester to form compounds having formula I, in which Y has the meaning of two hydrogen atoms.

The compounds ABC, in which R^{13} is a CH_2OSO_2alkyl group or CH_2OSO_2aryl group or CH_2OSO_2aralkyl and R^{20} represents a hydrogen atom, can be cyclized after deprotonation with suitable bases, for example, sodium hydride, n-butyllithium, 4-dimethylaminopyridine, Hünig base, alkylhexamethyldisilazanes, to form compounds having formula I, in which Y has the meaning of two hydrogen atoms.

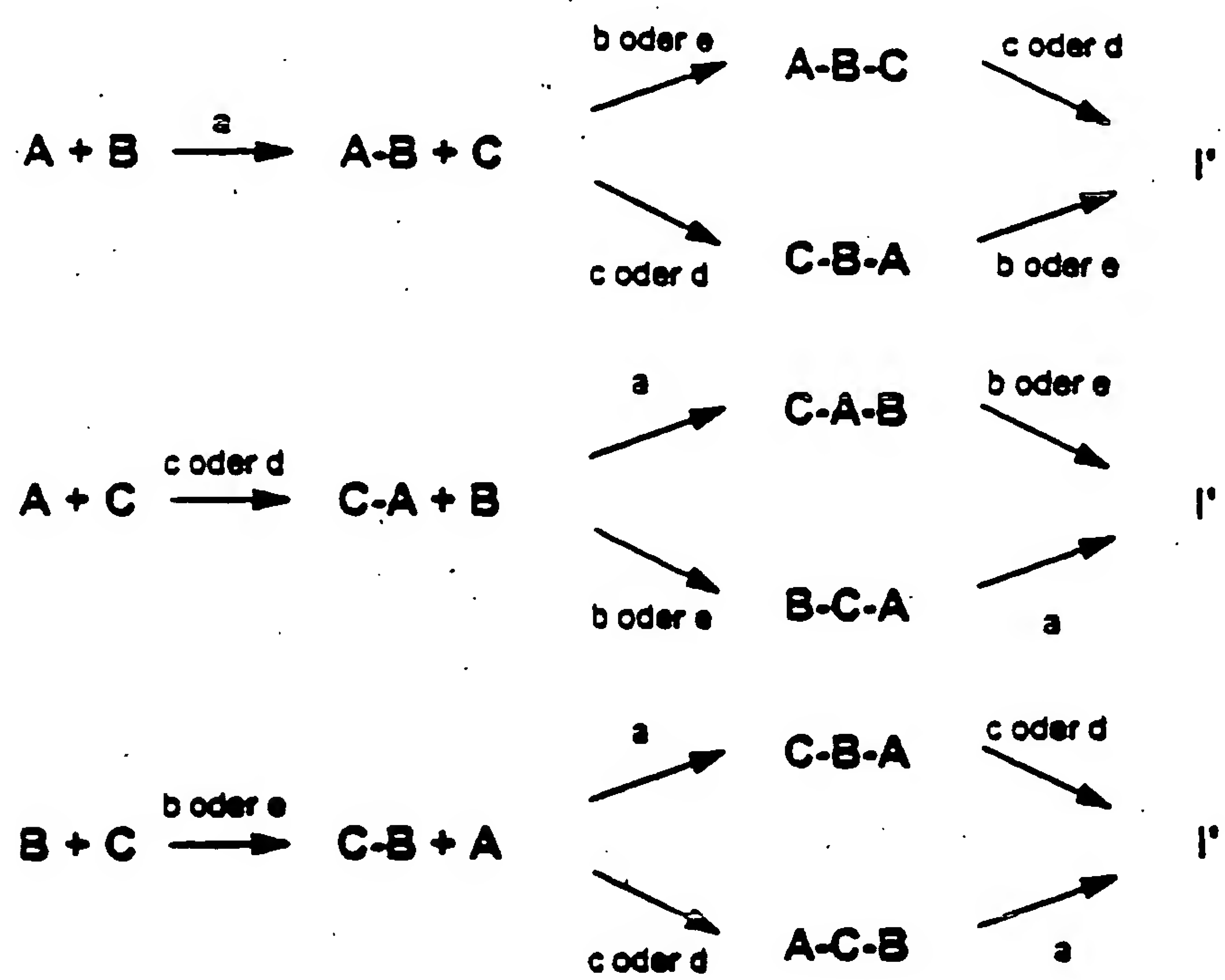
The flexible functionalization of the described building blocks A, B and C also provide a linking sequence which is different from the one described above, which leads to building blocks ABC. These methods are summarized in the following table:

linking possibilities	linking methods a to e	prerequisites
A + B → A-B	a: aldol (see Scheme 8)	Z = W = oxygen
B + C → B-C	b: Wittig (analogous to Scheme 9) e: McMurry	U = oxygen and R^{21} = Wittig salt or phosphine oxide or phosphonate U = V = oxygen
A + C → A-C	c: esterification (for example, 2,4,6-trichlorobenzoyl chloride/4-dimethylaminopyridine) d: etherification (for example, Mitsunobu)	R^{13} = CO_2R^{13b} or COHal and R^{20} = hydrogen R^{13} = CH_2OH and R^{20} = hydrogen or SO_2 alkyl or SO_2 aryl or SO_2 aralkyl

According to these methods, building blocks A, B and C can be linked, as shown in Scheme 10:

Scheme 10

Key: oder = or



Free hydroxyl groups in **I**, **A**, **B**, **C**, **AB**, **ABC** can be changed further functionally by etherification or esterification, and free carbonyl groups can be changed by ketalization, enol ether formation or reduction.

The invention concerns all stereoisomers of these compounds and also their mixtures.

Biological effects and areas of application of the new derivatives

The new compounds having formula I are valuable pharmaceuticals. They interact with tubulin, by stabilizing the formed microtubuli and are thus able to influence cell division in a phase-specific manner. This applies above all to fast-growing neoplastic cells, the growth of which is highly influenced by intercellular control mechanisms. Active ingredients of this type are, in principle, suitable for the treatment of malignant tumors. As an area of application, let us mention as example the therapy of ovarian, stomach, colon, adeno-, breast, lung, head and neck carcinomas, malignant melanoma, acute lymphocytary and myelocytary leukemia. Based on their properties, the compounds according to the invention are suitable in principle for antiangiogenesis therapy, as well as for the treatment of chronic inflammatory diseases, for example, psoriasis or arthritis. In order to avoid uncontrolled cell proliferation on medical implantates and to provide better compatibility of these, in principle, these can be applied onto or incorporated into the polymeric materials used. These compounds according to the invention can be used alone or, in order to achieve additive or synergistic effects, can be used in combination with other principles and substance classes that can be employed in tumor therapy.

As example, let us mention the combination with

- platinum complexes, for example, cisplatin, carboplatin,
- intercalating substances, for example, from the class of the anthracyclin, for example, doxorubicin or from the class of anthrapyrazoles, for example, CI-941,
- substances interacting with tubulin, for example, from the class of vinca-alkaloids, for example, vincristin, vinblastin or from the class of taxans, for example, taxol, taxoters or from the class of macrolids, for example, rhizoxin or other compounds, for example, colchicine, combretastatin A-4,
- DNA topoisomerase inhibitors, for example, camptothecin, etoposide, topotecan, teniposide,
- folate or pyrimidine antimetabolites, for example, lometrexol, gemcitubin,
- DNA alkylating compounds, for example, adozelesin, distamycin A,
- inhibitors of growth factors (for example, PDGF, EGF, TGFb, EGF), for example, somatostatin, suramin, bombesin antagonists,

- inhibitors of protein tyrosine kinase or protein kinases A or C, for example, erbstatin, genistein, staurosporin, limofosin, 8-Cl-cAMP,
- antihormones from the class of antigestagens, for example, mifepriston, onapriston or from the class of antiestrogens, for example, tamoxifen or from the class of anti-androgens, for example, cyproterone acetate,
- metastasis-inhibiting compounds, for example, from the class of eicosanoids, such as, for example, PGI_2, PGE_1, 6-Oxo-PGE_1 as well as their stable derivatives (for example, iloprost, cicaprost, misoprostol),
- inhibitors of oncogenic RAS proteins, which influence mitotic signal transduction, for example, inhibitors of farnesyl protein transferase,
- naturally or artificially produced antibodies, which are directed against receptors that promote tumor growth, for example, erbB2 antibody.

The invention is also concerned with drugs based on pharmaceutically compatible additives or carriers, that is, compounds which are not toxic at the doses used and have general formula I, optionally together with other additives and carriers.
The compounds according to the invention can be processed to according to known methods of galenics to pharmaceutical preparations for enteral, percutaneous, parenteral or local application. They can be administered in the form of tablets, coated tablets, gelcaps, granulates, suppositories, implantates, injectable sterile aqueous or oily solutions, suspensions or emulsions, salves, creams and gels.
The active ingredient(s) can be mixed with the usual additives in galenics, for example, gum arabic, talc, starch, mannitol, methylcellulose, lactose, surfactants, such as Tweens or myrj, magnesium stearate, aqueous or nonaqueous carriers, paraffin derivatives, wetting, dispersing, emulsifying agents, preservatives and aromas for correcting the taste (for example, essential oils).
Thus, the invention is also concerned with pharmaceutical composition, which contain at least one compound according to the invention as active ingredient. One dosage unit contains approximately 0.1-100 mg of active ingredient(s). The dosage of the compounds according to the invention lies for humans at about 0.1-1000 per day.

The following Examples serve to explain the invention further without representing any limitation:

Preparation of the building blocks according to general formula A from pantolactone or from malonic acid dialkyl esters:

Example 1

(3S)-1-oxa-2-oxo-3-(tetrahydropyran-2(RS)-yloxy)-4,4-dimethylcyclopentane

The solution of 74.1 g (569 mmole) on D-(-)pantolactone in 1 L of anhydrous dichloromethane is treated under an atmosphere of dry argon with 102 mL of 3,4-dihydro-2H-pyrane, 2 g of p-toluenesulfonic acid pyridinium salt and stirred for 16 hours at 23°C. The mixture is poured into a saturated sodium hydrogen carbonate solution, the organic phase is separated and dried over sodium sulfate. After filtration and the removal of solvent, the residue is chromatographed on approximately 5 kg of fine silica gel with a mixture of n-hexane and ethyl acetate. Thus, 119.6 g (558 mmole, 98%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.13 (3H), 1.22 (3H), 1.46-1.91 (6H), 3.50-3.61 (1H), 3.86 (1H), 3.92 (1H), 4.01 (1H), 4.16 (1H), 5.16 (1H) ppm.

Example 2

(2RS,3S)-1-Oxa-2-hydroxy-3-(tetrahydropyran-2(RS)-yloxy)-4,4-dimethylcyclopentane

The solution of 117.5 g (548 mmole) of the compound prepared according to Example 1 in 2.4 L of anhydrous toluene is cooled in an atmosphere of dry argon to -70°C and then 540 mL of a 1.2 molar solution of diisobutylaluminum hydride in toluene are added within 1 hour; the mixture is then stirred for 3 hours at -70°C. The mixture is allowed to warm up to -20°C, and the saturated ammonium chloride solution is added, water is added and the precipitated aluminum salts are separated by filtration through Celite. The filtrate is washed with water and saturated sodium chloride solution and dried over magnesium sulfate. After filtration and removal of the solvent, 111.4 g (515 mmole, 94%) of the compound in the title are isolated as a colorless oil, which is reacted without further purification.

IR ($CHCl_3$): 3480, 3013, 2950, 2874, 1262, 1133, 1074, 1026 and 808 cm^{-1}.

Example 3

(3S)-2,2-Dimethyl-3-(tetrahydropyran-2(R)-yloxy)-pent-4-en-1-ol and (3S)-2,2-dimethyl-3-(tetrahydropyran-2(S)-yloxy)-pent-4-en-1-ol

The suspension of 295 g of methyltriphenylphosphonium bromide in 2.5 L of anhydrous tetrahydrofuran is treated under a dry argon atmosphere at -60°C with 313 mL of a 2.4

molar solution of n-butyllithium in n-hexane. The mixture is allowed to warm up to 23°C and is stirred for another hour and then cooled to 0°C. Then a solution of 66.2 g (306 mmole) of the compound prepared in Example 2 in 250 mL of tetrahydrofuran, is added, the mixture is allowed to warm up to 23°C and is stirred for 18 hours. It is poured into a saturated sodium hydrogen carbonate solution, extracted several times with dichloromethane and the combined organic extracts are dried over sodium sulfate. After filtration and removal of the solvent, the residue is chromatographed on approximately 5 L of a fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 36.5 g (170 mmole, 56%) of the nonpolar and 14.4 g (67.3 mmole, 22%) of the polar THP isomer of the compound in the title are isolated as well as 7.2 g (33.3 mmole); 11%) of the starting material, each as a colorless oil.

^{1}H-NMR (CDCl$_3$), nonpolar isomer: δ = 0.78 (3H), 0.92 (3H), 1.41-1.58 (4H), 1.63-1.87 (2H), 3.18 (1H), 3.41 (1H), 3.48 (1H), 3.68 (1H), 3.94 (1H), 4.00 (1H), 4.43 (1H), 5.19 (1H), 5.27 (1H), 5.75 (1H) ppm.

^{1}H-NMR (CDCl$_3$), polar isomer: δ = 0.83 (3H), 0.93 (3H), 1.42-1.87 (6H), 2.76 (1H), 3.30 (1H), 3.45 (1H), 3.58 (1H), 3.83 (1H), 3.89 (1H), 4.65 (1H), 5.12-5.27 (2H), 5.92 (1H) ppm.

Example 4

(3S)-1-(tert.-Butyldiphenylsilyloxy)-2,2-dimethylpentane-3-(tetrahydropyran-2-yloxy)-pent-4-ene

The solution of 59.3 g (277 mmole) of the THP isomer mixture prepared in Example 3 in 1000 mL of anhydrous dimethylformamide is treated under a dry argon atmosphere with 28 g of imidazole, 85 mL of tert.-butyldiphenylchlorosilane and the mixture is stirred for 16 hours at 23°C. The mixture is poured into water, extracted several times with dichloromethane, the combined organic extracts are washed with water and dried over sodium sulfate. After filtration and removal of the solvent, the residue is chromatographed on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 106.7 g (236 mmole, 85%) of the title compound in the title are isolated as a colorless oil.

^{1}H-NMR (CDCl$_3$): δ = 0.89 (3H), 0.99 (3H), 1.08 (9H), 1.34-1.82 (6H), 3.40 (1H), 3.51 (2H), 3.76 (1H), 4.02 (1H), 4.67 (1H), 5.18 (1H), 5.23 (1H), 5.68 (1H), 7.30-7.48 (6H), 7.60-7.73 (4H) ppm.

Example 5

(3S)-1-(tert.-Butyldiphenylsilyloxy)-2,2-dimethyl-3-(tetrahydropyran-2-yloxy)-pentan-5-ol

The solution of 3.09 g (6.83 mmole) of the compound prepared according to Example 4 in 82 mL of tetrahydrofuran is treated under a dry argon atmosphere at 23°C with 13.1 mL of a 1 molar solution of borane in tetrahydrofuran and the mixture is allowed to react for 1 hour. Then, using cooling with ice, 16.4 mL of a 5% sodium hydroxide solution as well as 8.2 mL of a 30% hydrogen peroxide solution are added and stirring is continued for another 30 minutes. The mixture is poured into water, extracted several times with ethyl acetate, the combined organic extracts are washed with water, saturated sodium chloride solution and dried over magnesium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on a fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 1.78 g (3.78 mmole, 55%) of the compound in the title are isolated as a mixture of the two THP epimers that can be separated by chromatography as well as 0.44 g (1.14 mmole, 17%) of the compound in the title of Example 6 as a colorless oil.

^{1}H-NMR ($CDCl_3$), nonpolar THP isomer: δ = 0.80 (3H), 0.88 (3H), 1.10 (9H), 1.18-1.80 (9H), 3.27 (1H), 3.39 (1H), 3.48 (1H), 3.64 (1H), 3.83 (1H), 3.90-4.08 (2H), 4.49 (1H), 7.31-7.50 (6H), 7.58-7.73 (4H) ppm.

^{1}H-NMR ($CDCl_3$, polar THP isomer: δ = 0.89 (3H), 0.98 (3H), 1.08 (9H), 1.36-1.60 (4H), 1.62-1.79 (3H), 1.88 (1H), 2.03 (1H), 3.37 (1H), 3.50 (1H), 3.57 (1H), 3.62-3.83 (4H), 4.70 (1H), 7.30-7.48 (6H), 7.61-7.73 (4H) ppm.

Example 6

(3S)-1-(tert.-Butyldiphenylsilyloxy)-2,2-dimethylpentane-3,5-diol

The solution of 570 mg (1.55 mmole) of the compound prepared according to Example 12 is reacted in analogy to Example 5, and after processing and purification, 410 mg (1.06 mmole, 68%) of the compound in the title is isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$: δ = 0.82 (3H), 0.93 (3H), 1.08 (9H), 1.56-1.79 (2H), 3.11 (1H), 3.50 (2H), 3.78-3.92 (3H), 4.02 (1H), 7.34-7.51 (6H), 7.61-7.71 (4H) ppm.

Example 7

Variant I

4(S)-[2-Methyl-1-(tert.-butyldiphenylsilyloxy)-prop-2-yl]-2,2-dimethyl-[1,3]dioxane

The solution of 100 mg (0.212 mmole) of the compounds prepared according to Example 5 in 2.6 mL of anhydrous acetone is treated under an atmosphere of dry argon with 78.9 mg of copper(II) sulfate, a spatula-tip of p-toluenesulfonic acid monohydrate and the mixture is stirred for 16 hours at 23°C. Then, saturated sodium hydrogen carbonate solution is added, followed by extraction several times with diethyl ether, washing with saturated sodium chloride solution and drying over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 24 mg (56 μmole, 27%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.83 (3H), 0.89 (3H), 1.07 (9H), 1.30 (1H), 1.36 (3H), 1.44 (3H), 1.71 (1H), 3.24 (1H), 3.62 (1H), 3.86 (1H), 3.91-4.03 (2H), 7.31-7.48 (6H), 7.61-7.74 (4H) ppm.

Variant II

The compound prepared according to Example 6, 320 mg (0.88 mmole), is reacted in analogy to Example 7, Variant I, and, after work-up and purification, 234 mg (0.548 mmole, 62%) of the compound in the title are isolated.

Variant III

The solution of 5.60 g (14.5 mmole) of the compound prepared according to Example 6 in 250 mL of anhydrous dichloromethane is treated under a dry argon atmosphere with 10 mL of 2,2-dimethoxypropane, 145 mg of camphor-10-sulfonic acid and the mixture is stirred for 6 hours at 23°C. Triethylamine is added, the mixture is diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution and dried over sodium sulfate. After filtration and removal of the solvent, the residue os chromatographed on fine silica gel with a mixture of n-hexane and ethyl acetate. Thus, 5.52 g (12.9 mmole, 89%) of the compound in the title are isolated as a colorless oil.

Example 8

(4S)-4-(2-Methyl-1-hydroxyprop-2-yl)-2,2-dimethyl-[1,3]dioxane

A solution of 5.6 g (13.1 mmole) of the compound prepared according to Example 7 in 75 mL of tetrahydrofuran is treated under a dry argon atmosphere with 39 mL of a 1 molar solution of tetrabutylammonium fluoride in tetrahydrofuran and the mixture is heated for 16 hours at 50°C. Saturated sodium hydrogen carbonate solution is added, the mixture is extracted several times with ethyl acetate, washed with saturated sodium chloride solution and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 2.43 g (12.9 mmole, 99%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.87 (3H), 0.90 (3H), 1.35 (1H), 1.37 (3H), 1.43 (3H), 1.77 (1H), 2.93 (1H), 3.36 (1H), 3.53 (1H), 3.79 (1H), 3.87 (1H), 3.96 (1H) ppm.

Example 9

(4S)-4-(2-Methyl-1-oxo-prop-2-yl)-2,2-dimethyl-[1,3]dioxane

A solution of 0.13 mL of oxalyl chloride in 5.7 mL of anhydrous dichloromethane is cooled under a dry argon atmosphere to -70°C, followed by the addition of 0.21 mL of dimethylsulfoxide; the solution of 200 mg (1.06 mmole) of the compound prepared according to Example 8 in 5.7 mL of anhydrous dichloromethane is added and the mixture is stirred for 0.5 hours. Then, 0.65 mL of triethylamine are added, the mixture is allowed to react at -30°C for 1 hour and then treated with n-hexane and saturated sodium hydrogen carbonate solution. The organic phase is separated, the aqueous phase is extracted several times with n-hexane and the combined organic extracts are washed with water and dried over magnesium sulfate. The residue obtained after filtration and removal of the solvent is reacted without further purification.

Example 10

(4S)-4-(2-Methyl-3(RS)-hydroxypent-2-yl)-2,2-dimethyl-[1,3]dioxane

The solution of 900 mg (4.83 mmole) of the compound prepared according to Example 9 in 14 mL of anhydrous diethyl ether is treated under an atmosphere of dry argon at 0°C with 2.42 mL of a 2.4 molar solution of ethylmagnesium bromide in diethyl ether, the mixture is allowed to warm to 23°C and is stirred for 16 hours. Then, saturated ammonium chloride

solution is added, the organic phase is separated and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 321 mg (1.48 mmole, 31%) of the nonpolar 3R- or 3S epimers of the compound in the title, 542 mg (2.51 mmole, 52%) of the polar 3S- or 3R epimers of the compound in the title as well as 77 mg of the compound in the title of Example 8 are each obtained as a colorless oil.
^{1}H-NMR ($CDCl_3$) nonpolar isomer: δ = 0.86 (3H), 0.89 (3H), 1.03 (3H), 1.25-1.37 (2H), 1.37 (3H), 1.46 (3H), 1.49 (1H), 1.84 (1H), 3.35 (1H), 3.55 (1H), 3.81-4.02 (3H) ppm.
^{1}H-NMR ($CDCl_3$) polar isomer: δ = 0.72 (3H), 0.91 (3H), 0.99 (3H), 1.25-1.44 (2H), 1.38 (3H), 1.43-1.60 (1H), 1.49 (3H), 1.76 (1H), 3.39 (1H), 3.63 (1H), 3.79-4.03 (3H) ppm.

Example 11

(4S)-4-(2-Methyl-3-oxopent-2-yl)-2,2-dimethyl-[1,3]dioxane

The solution of 850 mg (3.93 mmole) of a mixture of the compounds prepared in Example 10 in 63 mL of anhydrous dichloromethane is treated with a molecular sieve (4A, approximately 80 beads), 690 mg of N-methylmorpholino-N-oxide, 70 mg of tetrapropylammonium perruthenate and the mixture is stirred for 16 hours at 23°C under an atmosphere of dry argon. The mixture is evaporated and the obtained crude product is purified by chromatography on approximately 200 mL of fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 728 mg (3.39 mmole, 86%) of the compound in the title are isolated as a colorless oil.
^{1}H-NMR ($CDCl_3$): δ = 1.00 (3H), 1.07 (3H), 1.11 (3H), 1.31 (1H), 1.32 (3H), 1.41 (3H), 1.62 (1H), 2.52 (2H), 3.86 (1H), 3.97 (1H), 4.05 (1H) ppm.

Example 12

(3S)-1-(tert.-Butyldiphenylsilyloxy)-2,2-dimethyl-3-hydroxypent-4-ene

A solution of 106.7 g (236 mmole) of the compound prepared according to Example 4 in 1.5 L of anhydrous ethanol is treated under a dry argon atmosphere with 5.9 g of pyridinium-p-toluenesulfonate and is heated for 6 hours at 50°C. After removal of the solvent, the residue is chromatographed on fine silica gel with a mixture of n-hexane and ethyl acetate. Thus, 82.6 g (224 mmole, 95%) of the compound in the title are isolated as a colorless oil, which additionally contains approximately 5 g of ethoxytetrahydropyrane.

^{1}H-NMR ($CDCl_3$) of an analytical sample: δ = 0.89 (6H), 1.08 (9H), 3.45 (1H), 3.49 (1H), 3.58 (1H), 4.09 (1H), 5.21 (1H), 5.33 (1H), 5.93 (1H), 7.34-7.51 (6H), 7.63-7.73 (4H) ppm.

Example 13

(4S)-4-((2RS)-3-Methyl-2-hydroxyprop-3-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 10, 450 mg (2.42 mmole) of the compound prepared according to Example 9 are reacted using methylmagnesium bromide. After processing and purification, one isolates 431 mg (2.13 mmole, 88%) of a chromatographically separable mixture of the epimeric compounds in the title as colorless oil.

Example 14

(4S)-4-(3-Methyl-2-oxoprop-3-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 11, 420 mg (2.08 mmole) of the compounds prepared according to Example 13 are reacted. After processing and purification, 388 mg (1.94 mmole, 93%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.08 (3H), 1.12 (3H), 1.33 (3H), 1.35 (1H), 1.42 (3H), 1.63 (1H), 2.17 (3H), 3.87 (1H), 3.98 (1H), 4.04 (1H) ppm.

Example 15

(4S)-4-((3RS)-2-Methyl-3-hydroxyhex-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 10, 450 mg (2.42 mmole) of the compound prepared according to Example 9 are reacted using n-propylmagnesium bromide. After processing and purification, a total of 244 mg (1.06 mmole, 44%) of a separable mixture of the epimeric compounds in the title as well as 191 mg of the compound in the title of Example 8, are isolated, each as a colorless oil.

^{1}H-NMR ($CDCl_3$) nonpolar isomer: δ = 0.87 (3H), 0.89 (3H), 0.94 (3H), 1.25-1.52 (4H), 1.38 (3H), 1.45 (3H), 1.66 (1H), 1.85 (1H), 3.46 (1H), 3.80-4.02 (4H) ppm.

^{1}H-NMR ($CDCl_3$) polar isomer: δ = 0.73 (3H), 0.92 (3H), 0.95 (3H), 1.19-1.84 (6H), 1.37 (3H), 1.49 (3H), 3.49 (1H), 3.60 (1H), 3.80-4.03 (3H) ppm.

Example 16

(4S)-4-(2-Methyl-3-oxohex-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 11, 230 mg (1.00 mmole) of the compounds prepared according to Example 15 are reacted. After processing and purification, 185 mg (0.81 mmole, 81%) of the compound in the title are isolated as colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.88 (3H), 1.04 (3H), 1.12 (3H), 1.22-1.37 (1H), 1.31 (3H), 1.40 (3H), 1.48-1.71 (3H), 2.46 (2H), 3.83 (1H), 3.96 (1H), 4.04 (1H) ppm.

Example 17

(4R)-4-(2-Methyl-3-oxopent-2-yl)-2,2-dimethyl-[1,3]dioxane

Starting from L-(+)-pantolactone, in analogy to the method described in Examples 1 to 9 and 12, the compound in the title is prepared through the respective enantiomeric intermediate steps.

^{1}H-NMR ($CDCl_3$): δ = 1.00 (3H), 1.07 (3H), 1.12 (3H), 1.24-1.37 (1H), 1.31 (3H), 1.40 (3H), 1.61 (1H), 2.50 (2H), 3.84 (1H), 3.95 (1H), 4.03 (1H) ppm.

Example 18

(4R)-4-(3-Methyl-2-oxoprop-3-yl)-2,2-dimethyl-[1,3]dioxane

Starting from L-(+)-pantolactone, in analogy to the method described in Examples 1 to 9 and 12 to 14, the compound in the title is prepared through the respective enantiomeric intermediate steps.

^{1}H-NMR ($CDCl_3$): δ = 1.07 (3H), 1.12 (3H), 1.30-1.39 (1H), 1.33 (3H), 1.43 (3H), 1.62 (1H), 2.17 (3H), 3.86 (1H), 3.96 (1H), 4.03 (1H) ppm.

Example 19

(4R)-4-(2-Methyl-3-oxohex-2-yl)-2,2-dimethyl-[1,3]dioxane

Starting from L-(+)-pantolactone, in analogy to the method described in Examples 1 to 9, 12, 15 and 16, the compound in the title is prepared through the respective enantiomeric intermediate steps.

^{1}H-NMR ($CDCl_3$): δ = 0.88 (3H), 1.04 (3H), 1.12 (3H), 1.22-1.37 (1H), 1.31 (3H), 1.41 (3H), 1.48-1.72 (3H), 2.47 (2H), 3.84 (1H), 3.96 (1H), 4.05 (1H) ppm.

Example 20

[2S,4S)-2-(2-Cyanophenyl)-4-[2-methyl-1-(tert.-butyldiphenylsilyloxy)-prop-2-yl]-[1,3]-dioxane

A solution of 1.00 g (2.59 mmole) of the compound prepared in Example 6 in 50 mL of benzene is treated with 850 mg of 2-cyanobenzaldehyde, a spatula-tip of p-toluenesulfonic acid monohydrate and refluxed for 16 hours on a water-separator under a dry argon atmosphere. Then 0.5 mL of triethylamine diluted with ethyl acetate are added, followed by washing with saturated sodium hydrogen carbonate solution and drying over sodium sulfate. After filtration and removal of the solvent, the residue is chromatographed on fine silica gel with a mixture of n-hexane and ethyl acetate. Thus, 1.22 g (2.44 mmole, 94%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.99 (6H), 1.05 (9H), 1.47 (1H), 1.98 (1H), 3.34 (1H), 3.63 (1H), 3.96-4.09 (2H), 4.31 (1H), 5.75 (1H), 7.17 (2H), 7.24-7.51 (5H), 7.51-7.74 (7H) ppm.

Example 21

(2S,4S)-2-(2-Cyanophenyl)-4-(2-methyl-1-hydroxyprop-2-yl)-[1,3]dioxane

In analogy to Example 8, 1.22 g (2.44 mmole) of the compound prepared according to Example 20 is reacted and, after work-up and purification, 593 mg (2.27 mmole, 93%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.89 (3H), 0.97 (3H), 1.51 (1H), 2.01 (1H), 2.42 (1H), 3.31 (1H), 3.72 (1H), 3.97 (1H), 4.02 (1H), 4.39 (1H), 5.78 (1H), 7.46 (1H), 7.63 (1H), 7.69 (1H), 7.75 (1H) ppm.

Example 22

(2S,4S)-2-(2-Cyanophenyl)-4-(2-methyl-1-oxopro-2-yl)-[1,3]dioxane

In analogy to Example 9, 570 mg (2.18 mmole) of the compound prepared according to Example 21 is reacted and, after work-up, 780 mg of the compound in the title are isolated as a yellow oil, which is reacted further without purification.

Example 23

(2S,4S)-2-(2-Cyanophenyl)-4-((3RS)-2-methyl-3-hydroxypent-2-yl)-[1,3]dioxane

In analogy to Example 10, 780 g (maximum 2.18 mmole) of the crude product prepared according to Example 22 is reacted and, after work-up and purification, 468 mg (1.62 mmole, 74%) of the epimeric compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.81-1.09 (9H), 1.22-1.43 (1H), 1.43-1.70 (2H), 2.04 (1H), 2.35 (0.55H), 2.89 (0.45H), 3.41-3.59 (1H), 3.89-4.13 (2H), 4.36 (1H), 5.78 (0.45H), 5.81 (0.55H), 7.45 (1H), 7.54-7.78 (3H) ppm.

Example 24

(2S,4S)-2-(2-Cyanophenyl)-4-(2-methyl-3-oxopent-2-yl)-[1,3]dioxane

In analogy to Example 11, 463 mg (1.60 mmole) of the compound prepared according to Example 23 are reacted and, after work-up and purification, 420 mg (1.46 mmole, 91%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.00 (3H), 1.19 (3H), 1.24 (3H), 1.49 (1H), 1.92 (1H), 2.56 (2H), 4.03 (1H), 4.16 (1H), 4.32 (1H), 5.78 (1H), 7.44 (1H), 7.60 (1H), 7.64-7.72 (2H) ppm.

Example 25

(4S,2S)-4-[2-Methyl-1-(tert.-butyldiphenylsilyloxy)-prop-2-yl]-2-phenyl-[1,3]dioxane

In analogy to Example 20, 1,00 g (2.59 mmole) of the compound prepared according to Example 6 is reacted in 50 mL of toluene using benzaldehyde, and, after work-up and purification, 1.2 g (2.53 mmole, 98%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.93 (3H), 1.00 (3H), 1.07 (9H), 1.43 (1H), 1.92 (1H), 3.30 (1H), 3.72 (1H), 3.95 (1H), 4.00 (1H), 4.30 (1H), 5.53 (1H), 7.18 (2H), 7.29-7.49 (9H), 7.61 (2H), 7.67 (2H) ppm.

Example 26

(4S,2S)-4-(2-Methyl-1-hydroxyprop-2-yl)-2-phenyl-[1,3]dioxane

In analogy to Example 8, 1.20 g (2.53 mmole) of the compound prepared according to Example 25 is reacted and, after work-up and purification, 518 mg (2.19 mmole, 87%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.98 (6H), 1.49 (1H), 2.00 (1H), 2.49 (1H), 3.46 (1H), 3.62 (1H), 3.81 (1H), 3.98 (1H), 4.33 (1H), 5.51 (1H), 7.30-7.41 (3H), 7.41-7.51 (2H) ppm.

Example 27

(2S,4S)-4-(2-Methyl-1-oxyprop-2-yl)-2-phenyl-[1,3]dioxane

In analogy to Example 9, 500 mg (2.12 mmole) of the compound prepared according to Example 26 are reacted and, after work-up, 715 mg of the title compound are isolated as a yellow oil, which is reacted further without purification.

Example 28

(2S,4S)-4-((3RS)-2-Methyl-3-hydroxypent-2-yl)-2-phenyl-[1,3]dioxane

In analogy to Example 10, 715 mg (maximum 2.12 mmole) of the crude product prepared according to Example 27 are reacted and, after work-up and purification, 440 mg (1.66 mmole, 79%) of the epimeric compounds in the title are isolated as a colorless oil.
^{1}H-NMR ($CDCl_3$): δ = 0.80-1.10 (9H), 1.23-1.42 (1H), 1.42-1.70 (2H), 1.90-2.16 (1H), 2.92 (0.6H), 3.07 (0.4H), 3.40-3.53 (1H), 3.86 (1H), 3.98 (1H), 4.32 (1H), 5.49 (0.4H), 5.55 (0.6H), 7.28-7.40 (3H), 7.40-7.51 (2H) ppm.

Example 29

(2S,4S)-4-(2-Methyl-3-oxopent-2-yl)-2-phenyl-[1,3]dioxane

In analogy to Example 11, 435 mg (1.65 mmole) of the compound prepared according to Example 28 are reacted and, after work-up and purification, 410 mg (1.56 mmole, 95%) of the compound in the title are isolated as a colorless oil.
^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.17 (3H), 1.23 (3H), 1.44 (1H), 1.84 (1H), 2.58 (2H), 3.97 (1H), 4.06 (1H), 4.30 (1H), 5.50 (1H), 7.28-7.49 (5H) ppm.

Example 30

(4S)-4-[2-Methyl-1-(tert.-butyldiphenylsilyloxy)-prop-2-yl]-2,2-pentamethylene-[1,3]dioxane

In analogy to Example 20, 1.00 g (2.59 mmole) of the compound prepared according to Example 6 is reacted in 50 mL of toluene using cyclohexanone and, after work-up and

purification, 1.09 g (2.34 mmole, 90%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.84 (3H), 0.89 (3H), 0.97-1.10 (10H), 1.20-1.64 (9H), 1.71 (1H), 2.13 (1H), 3.33 (1H), 3.56 (1H), 3.81 (1H), 3.89 (1H), 3.99 (1H), 7.32-7.49 (6H), 7.60-7.74 (4H) ppm.

Example 31

(4S)-4-(2-Methyl-1-hydroxyprop-2-yl)-2,2-pentamethylene-[1,3]dioxane

In analogy to Example 8, 1.09 g (2.34 mmole) of the compound prepared according to Example 30 is reacted and, after work-up and purification, 470 mg (2.06 mmole, 88%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.88 (3H), 0.94 (3H), 1.24-1.71 (10H), 1.81 (1H), 2.18 (1H), 3.09 (1H), 3.39 (1H), 3.60 (1H), 3.80 (1H), 3.87 (1H), 4.02 (1H) ppm.

Example 32

(4S)-4-(2-Methyl-1-oxoprop-2-yl)-2,2-pentamethylene-[1,3]dioxane

In analogy to Example 9, 450 mg (1.97 mmole) of the compound prepared according to Example 31 is reacted and, after work-up, 678 mg of the compound in the title are isolated as a yellow oil which is reacted further without purification.

Example 33

(4S)-4-(2-Methyl-3-hydroxypent-2-yl)-2,2-pentamethylene-[1,3]dioxane

In analogy to Example 10, 678 mg (maximum 1.97 mmole) of the crude product prepared according to Example 32 is reacted and, after work-up and purification, 391 mg (1.54 mmole, 77%) of the epimeric compounds in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.70-1.08 (9H), 1.23-1.98 (13H), 2.01-2.13 (1H), 3.37-3.50 (1H), 3.61 (0.5H), 3.80-4.06 (3.5H) ppm.

Example 34

(4S)-(2-Methyl-3-oxopent-2-yl)-2,2-pentamethylene-[1,3]dioxane

In analogy to Example 11, 386 mg (1.51 mmole) of the compound prepared according to Example 33 are reacted and, after work-up and purification, 376 mg (1.48 mmole, 98%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.09 (3H), 1.17 (3H), 1.22-1.38 (3H), 1.40-1.72 (8H), 2.15 (1H), 2.57 (2H), 3.81 (1H), 3.92-4.07 (2H) ppm.

Example 35

(4S)-4-[2-Methyl-1-(tert.-butyldiphenylsilyloxy)-prop-2-yl]-2,2-tetramethylene-[1,3]dioxane

In analogy to Example 20, 1.00 g (2.59 mmole) of the compound prepared according to Example 6 in 50 mL of toluene is reacted using cyclopentanone and, after work-up and purification, 997 mg (2.20 mmole, 85%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.84 (3H), 0.88 (3H), 0.99-1.10 (10H), 1.30 (1H), 1.50-1.99 (8H), 3.23 (1H), 3.60 (1H), 3.80-3.98 (3H), 7.31-7.49 (6H), 7.61-7.73 (4H) ppm.

Example 36

(4S)-4-(2-Methyl-1-hydroxyprop-2-yl)-2,2-tetramethylene-[1,3]dioxane

In analogy to Example 8, 997 mg (2.20 mmole) of the compound prepared according to Example 35 are reacted and, after work-up and purification, 415 mg (1.94 mmole, 88%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.90 (6H), 1.36 (1H), 1.53-2.02 (9H), 2.93 (1H), 3.39 (1H), 3.55 (1H), 3.70 (1H), 3.87 (1H), 3.96 (1H) ppm.

Example 37

(4S)-4-(2-Methyl-1-oxoprop-2-yl)-2,2-tetramethylene-[1,3]dioxane

In analogy to Example 9, 400 mg (1.87 mmole) of the compound prepared according to Example 36 are reacted and, after work-up, 611 mg of the compound in the title are isolated as a yellow oil, which is further reacted without purification.

Example 38

(4S)-4-(2-Methyl-3-hydroxypent-2-yl)-2,2-tetramethylene-[1,3]dioxane

In analogy to Example 10, 611 mg (maximum 1.87 mmole) of the compound prepared according to Example 37 are reacted, and, after work-up and purification, 353 mg (1.46 mmole, 78%) of the epimeric compounds in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.71-1.09 (9H), 1.20-1.44 (2H), 1.44-1.78 (5H), 1.78-2.02 (5H), 3.32-3.44 (1H), 3.51-3.60 (1H), 3.76 (1H), 3.80-4.02 (2H) ppm.

Example 39

(4S)-4-(2-Methyl-3-oxopent-2-yl)-2,2-tetramethylene-[1,3]dioxane

In analogy to Example 11, 348 mg (1.44 mmole) of the compound prepared according to Example 38 are reacted, and, after work-up and purification, 332 mg (1.38 mmole, 96%) of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCL_3$): δ = 1.00 (3H), 1.07 (3H), 1.17 (3H), 1.31 (1H), 1.50-2.00 (9H), 2.52 (2H), 3.84 (1H), 3.88-3.99 (2H) ppm.

Example 40

1,1-Cyclobutanedimethanol

To a solution of 20 g (99.9 mmole) of 1,1-cyclobutanedicarboxylic acid diethyl ester in 200 mL of absolute tetrahydrofuran, 170 mL of a 1.2 molar solution of diisobutylaluminum hydride are added dropwise at 0°C. The mixture is stirred further for one hour at 0°C and then 30 mL of water are added. It is filtered through Celite. The filtrate is dried with sodium sulfate and evaporated in vacuum. The obtained crude product (9.9 g, 85.2 mmole, 85%) is used in the next step without any purification.

Example 41

1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutanemethanol

To a suspension of 3.4 g of sodium hydride (60% in oil) in 35 mL of absolute tetrahydrofuran, a solution of 9.9 g (85 mmole) of the compound prepared according to Example 40 in 100 mL of absolute tetrahydrofuran are added at 0°C. Stirring is continued for 30 minutes and then a solution of 12.8 g of *tert.*-butyldimethylsilyl chloride in 50 mL of tetrahydrofuran is added. The mixture is stirred for another hour at 25°C and then the reaction mixture is poured into saturated aqueous sodium hydrogen carbonate solution. The mixture is extracted with ethyl acetate. The organic phase is washed with saturated sodium chloride solution and dried over sodium sulfate. After removal of the solvent in vacuum, the obtained crude product is purified by column chromatography on silica gel with a mixture of hexane/ethyl acetate. Thus, 13.5 g (58.6 mmole, 69%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.04 (6H), 0.90 (9H), 1.70-2.00 (6H), 3.70 (4H) ppm.

Example 42

1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutanecarbaldehyde

Oxalyl chloride, 8 mL, is dissolved in 100 mL of dichloromethane. It is cooled to -78°C and 13 mL of dimethylsulfoxide are added. Stirring is continued for 3 minutes and then a solution of 13.5 g (58.6 mmole) of the compound prepared according to Example 41 in 80 mL of dichloromethane are added. After another 15 minutes of stirring time, 58 mL of triethylamine are added dropwise. Then the mixture is allowed to warm up to 0°C. The reaction mixture is poured into saturated sodium hydrogen carbonate solution. This is extracted with dichloromethane. Then the mixture is allowed to warm up to 0°C. The reaction mixture is poured into saturated sodium hydrogen carbonate solution. This is extracted with dichloromethane, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After chromatography of the crude product on silica gel with a mixture of hexane/ethyl acetate, 7.7 g (33.7 mmole, 58%) of the compound in the title are obtained.

^{1}H-NMR (CDCl$_3$: δ = 9.70 s (1H), 3.83 s (2H), 2.20-2.30 m (2H), 1.85-2.00 m (4H), 0.90 s (9H), 0.03 s (6H) ppm.

Example 43

[1*R*-[1α(*R),2β]]-2-Phenylcyclohexyl 3-[1-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]-cyclobutyl]-3-hydroxypropanoate (A) and**

[1*R*-[1α(*S),2β]]-2-Phenylcyclohexyl 3-[1-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]-cyclobutyl]-3-hydroxypropanoate (B)**

Starting from 7.2 mL of diisopropylamine and butyllithium (32 mL of a 1.6 molar solution in hexane), lithium diisopropylamide was prepared in absolute tetrahydrofuran. Then, at -78°C, a solution of 11.2 g (1*R-trans*)-2-phenylcyclohexyl acetate in 100 mL of absolute tetrahydrofuran is added and the mixture is stirred at this temperature for 30 minutes. Then a solution of 7.7 g (33.7 mmole) of the compound prepared according to Example 42 in 50 mL of tetrahydrofuran are added. The mixture is stirred for 1.5 hours at -78°C and then it is poured into saturated aqueous ammonium chloride solution. This is extracted with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and is evaporated in vacuum. After chromatography of the crude product on silica gel by column chromatography with a mixture of hexane/ethyl acetate, 6.34 g (14.2

mmole, 42%) of the compound A in the title and 4.22 g (9.4 mmole, 28%) of compound B in the title are obtained.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.04 (6H), 0.98 (9H), 2.69 (1H), 3.08 (1H), 3.60 (1H), 3.67 (1H), 3.78-3.84 (1H), 4.97 (1H), 7.15-7.30 (5H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.03 (6H), 0.90 (9H), 2.68 (1H), 2.80 (1H), 3.56 (2H), 3.68-3.72 (1H), 4.99 (1H), 7.18-7.30 m (5H) ppm.

Example 44

(S)-1-[1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutyl]-1,3-propanediol

To a solution of 1 g (2.24 mmole) of compound A prepared according to Example 43 in 10 mL of absolute toluene, 4 mL of a 1.2 molar solution of diisobutylaluminum hydride in toluene are added dropwise at 0°C. The mixture is stirred for 1.5 hours at 0°C and then 5 mL of water are added. The mixture is filtered through Celite. The filtrate is dried over sodium sulfate and evaporated in vacuum. After chromatography of the crude product on silica gel in a column with a mixture of hexane/ethyl acetate, 370 mg (1.35 mmole, 60%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.05 (6H), 0.90 (9H), 1.55-1.60 (2H), 1.80 (2H), 1.90 (3H), 2.10 (1H), 3.75 (1H), 3.85-3.95 (4H) ppm.

Example 45

(S)-2,2-Dimethyl-4-[1-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutyl]-1,3-dioxane

The compound prepared according to Example 44, 370 mg (1.35 mmole), is dissolved in 10 mL of acetone. A spatula tip of p-toluenesulfonic acid is added and the mixture is stirred for 2 hours at 25°C. Then the reaction mixture is poured into saturated sodium hydrogen carbonate solution. The mixture is extracted with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After column chromatography on silica gel with a mixture of hexane/ethyl acetate, 338 mg (1.07 mmole), 79%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.03 (6H), 0.88 (9H), 1.38 (3H), 1.42 (3H), 1.50-1.80 (4H), 2.00 (1H), 3.52 (1H), 3.62 (1H), 3.85-4.00 (3H) ppm.

Example 46

(R)-1-[1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutyl]-1,3-propanediol

In analogy to Example 44, 700 mg (1.57 mmole) of compound B prepared according to Example 43 are reacted, and, after work-up and purification, 250 mg (0.91 mmole, 58%) of the compound in the title are obtained.

The ^{1}H-NMR spectrum is superimposable with that described in Example 44.

Example 47

(*R*)-2,2-Dimethyl-4-[1-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutyl]-1,3-dioxane

In analogy to Example 45, 250 mg (0.91 mmole) of the compound prepared according to Example 46 is reacted, and, after work-up and purification, 228 mg (0.72 mmole, 60%) of the compound in the title are obtained.

The ^{1}H-NMR spectrum is superimposable with that described in Example 45.

Example 48

1-[1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutyl]-1,3-propanediol

In analogy to Example 44, 500 mg (1.12 mmole) of a mixture of compounds A and B, prepared according to Example 43, are reacted, and, after work-up and purification, 190 mg (0.69 mmole, 62%) of the compound in the title are obtained.

The ^{1}H-NMR spectrum is superimposable with that described in Example 44.

Example 49

2,2-Dimethyl-4-[1-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutyl]-1,3-dioxane

In analogy to Example 45, 190 mg (0.69 mmole) of the compound prepared according to Example 48 are reacted, and, after work-up and purification, 171 mg (0.54 mmole, 79%) of the compound in the title are obtained.

The ^{1}H-NMR spectrum is superimposable with that described in Example 45.

Example 50

[1*R*-[1α(3*S),2β]]-2-Phenylcyclohexyl-3-[1-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]-methyl]cyclobutyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propanoate**

In analogy to Example 1, 460 mg (1.03 mmole) of the compound prepared according to Example 43 is reacted, and, after work-up and purification, 398 mg (0.75 mmole, 73%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.01 (6H), 0.89 (9H), 1.24-1.97 (19H), 2.15-2.27 (3H), 2.66 (1H), 3.12 (1H), 3.50 (2H), 3.58 (1H), 3.98 (1H), 4.52 (1H), 4.87 (1H), 7.09-7.27 (5H) ppm.

Example 51

(*S*)-3-[1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propanoic acid

Potassium tert.-butylate, 420 mg (3.75 mmole), is suspended in 5 mL of diethyl ether. Then, 16 μL of water are added and stirring is continued for 5 minutes. Then a solution of 398 mg (0.75 mmole) of the compound prepared according to Example 50 in 5 mL of diethyl ether are added. Stirring is continued for 3 hours. Then the reaction mixture is diluted with water and neutralized with 10% hydrochloric acid. It is extracted with dichloromethane, the organic phase is washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. Column chromatography of the crude product on silica gel with a mixture of hexane/ethyl acetate gives 112 mg (0.3 mmole).

^{1}H-NMR ($CDCl_3$): δ = 0.01 (6H), 0.90 (9H), 1.30-2.25 (10H), 3.12 (1H), 3.50 (2H), 3.58 (1H), 3.98 (1H), 4.45 (1H) ppm.

After cleaving off the silyl protective group by oxidation, the reaction product can be converted to the aldehyde analogously to Example 9, reacted analogously to Example 10 with an organometallic compound, such as, for example, $XMgCHR^{5a}R^{5b}$, for example, with ethyl magnesium bromide, and converted into compounds according to Claim 1 by subsequent oxidation of the obtained alcohol mixture analogously to Example 11.

If, in Example 40, the starting material, 1,1-cyclobutanedicarboxylic acid ethyl ester is replaced by other 2-substituted or 2,2-disubstituted malonic ester derivatives, for example, the following compounds can be prepared in analogy to Examples 9, 10 and 40-51:

R^{4a}	R^{4b}	R^{5a}	R^{5b}
$-(CH_2)_2-$		H	CH_3
$-(CH_2)_2-$		H	CH_2-CH_3
$-(CH_2)_2-$		H	$(CH_2)_2-CH_3$
$-(CH_2)_2-$		H	$CH_2-C_6H_5$
$-(CH_2)_2-$		H	$(CH_2)_2-C_6H_5$
$-(CH_2)_2-$		CH_3	CH_3
$-(CH_2)_2-$		CH_3	CH_2-CH_3
$-(CH_2)_3-$		H	CH_3
$-(CH_2)_3-$		H	CH_2-CH_3
$-(CH_2)_3-$		H	$(CH_2)_2-CH_3$
$-(CH_2)_3-$		H	$CH_2-C_6H_5$
$-(CH_2)_3-$		H	$(CH_2)_2-C_6H_5$
$-(CH_2)_3-$		CH_3	CH_3
$-(CH_2)_3-$		CH_3	CH_2-CH_3
$-(CH_2)_4-$		H	CH_3
$-(CH_2)_4-$		H	CH_2-CH_3
$-(CH_2)_4-$		H	$(CH_2)_2-CH_3$
$-(CH_2)_4-$		H	$CH_2-C_6H_5$
$-(CH_2)_4-$		H	$(CH_2)_2-C_6H_5$
$-(CH_2)_4-$		CH_3	CH_3
$-(CH_2)_4-$		CH_3	CH_2-CH_3
CH_3	CH_3	H	CH_3
CH_3	CH_3	CH_2-CH_3	CH_2-CH_3
CH_3	CH_3	H	$(CH_2)_2-CH_3$
CH_3	CH_3	H	$CH_2-C_6H_5$
CH_3	CH_3	H	$(CH_2)_2-C_6H_5$
CH_2-CH_3	CH_2-CH_3	H	CH_3
CH_2-CH_3	CH_2-CH_3	H	CH_2-CH_3
CH_2-CH_3	CH_2-CH_3	H	$(CH_2)_2-CH_3$
CH_2-CH_3	CH_2-CH_3	H	$CH_2-C_6H_5$
CH_2-CH_3	CH_2-CH_3	H	$(CH_2)_2-C_6H_5$
CH_3	CH_2-CH_3	H	CH_3
CH_3	CH_2-CH_3	H	CH_2-CH_3
CH_3	CH_2-CH_3	H	$(CH_2)_2-CH_3$
CH_3	CH_2-CH_3	H	$CH_2-C_6H_5$
CH_3	CH_2-CH_3	H	$(CH_2)_2-C_6H_5$

Example 52

(3S)-4,4-Dimethyl-5-oxo-3-(tetrahydropyran-2-yloxy)-pent-1-ene

In analogy to Example 9, 5.0 g (23.3 mmole) of the compound prepared according to Example 3 are reacted, and, after work-up, 6.1 g of the compound in the title is isolated as a colorless oil, which is reacted further without purification.

Example 53

(3S,5RS)-4,4-Dimethyl-5-hydroxy-3-(tetrahydropyran-2-yloxy)-hept-1-ene

In analogy to Example 10, 6.1 g (maximum 23.3 mmole) of the crude product prepared according to Example 52 are reacted, and, after work-up and purification, 1.59 g (6.56 mmole, 28%) of the nonpolar diastereomer as well as 1.67 g (6.89 mmole, 30%) of the polar diastereomer are isolated, each as a colorless oil.

^{1}H-NMR ($CDCl_3$) nonpolar isomer: δ = 0.79 (3H), 0.84 (3H), 1.03 (3H), 1.23-1.62 (6H), 1.62-1.88 (2H), 3.41-3.58 (2H), 3.88-4.01 (2H), 4.08 (1H), 4.47 (1H), 5.20 (1H), 5.29 (1H), 5.78 (1H) ppm.

^{1}H-NMR ($CDCl_3$) polar isomer: δ = 0.78 (3H), 0.93 (3H), 1.01 (3H), 1.38 (1H), 1.47-1.85 (7H), 3.39-3.57 (3H), 3.90 (1H), 4.04 (1H), 4.62 (1H), 5.21 (1H), 5.32 (1H), 5.69 (1H) ppm.

Example 54

(3S,5S)-4,4-Dimethyl-3-(tetrahydropyran-2-yloxy)-heptane-1,5-diol and/or (3S,5R)-4,4-dimethyl-3-(tetrahydropyran-2-yloxy)-heptane-1,5-diol

In analogy to Example 5, 1.59 g (6.56 mmole) of the nonpolar alcohol prepared according to Example 53 are reacted, and, after work-up, 1.14 g (4.38 mmole, 67%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.78 (6H), 1.01 (3H), 1.28 (1H), 1.36-1.64 (6H), 1.64-1.93 (4H), 3.41-3.55 (2H), 3.61-3.82 (2H), 3.87 (1H), 3.99 (1H), 4.28 (1H), 4.56 (1H) ppm.

Example 55

(3S,5R or 5S)-1-Benzoyloxy-4,4-dimethyl-3-(tetrahydropyran-2-yloxy)-heptan-5-ol

The solution of 1.04 g (3.99 mmole) of the compound prepared according to Example 54 in 20 mL of anhydrous pyridine is treated in a dry argon atmosphere with 476 μL of benzoyl chloride, followed by stirring for 16 hours at 23°C. The mixture is poured into a saturated

sodium hydrogen carbonate solution, extracted with dichloromethane and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on approximately 300 mL of fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 785 mg (2.15 mmole, 54%) of the compound in the title as a colorless oil as well as 352 mg of starting material are isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.83 (6H), 1.04 (3H), 1.31 (1H), 1.38-1.58 (5H), 1.74-1.99 (3H), 2.12 (1H), 3.40 (1H), 3.52 (1H), 3.90-4.03 (2H), 4.28-4.56 (4H), 7.45 (2H), 7.58 (1H), 8.05 (2H) ppm.

Example 56

(3S)-1-Benzoyloxy-4,4-dimethyl-3-(tetrahydropyran-2-yloxy)-heptan-5-one

In analogy to Example 11, 780 mg (2.14 mmole) of the compound prepared according to Example 55 is reacted, and, after work-up and purification, 641 mg (1.77 mmole, 83%) of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.11 (3H), 1.23 (3H), 1.40-1.56 (4H), 1.65-1.87 (3H), 1.93 (1H), 2.59 (2H), 3.36 (1H), 3.80 (1H), 4.13 (1H), 4.32 (1H), 4.45 (1H), 4.53 (1H), 7.45 (2H), 7.58 (1H), 8.05 (2H) ppm.

Example 57

(3S)-1-Hydroxy-4,4-dimethyl-3-(tetrahydropyran-2-yloxy)-heptan-5-one

A solution of 636 mg (1.75 mmole) of the compound prepared according to Example 56 in 25 mL of methanol is treated with 738 mg of potassium carbonate and the mixture is stirred for 2 hours at 23°C. Dichloromethane is added, the mixture filtered, washed with water and the organic phase dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on approximately 100 mL of fine silica gel with an n-hexane and ethyl acetate gradient system. Thus, 311 mg (1.20 mmole, 69%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.98 (3H), 1.07 (3H), 1.18 (3H), 1.44-1.90 (10H), 2.00 (1H), 3.50-3.68 (2H), 3.74 (1H), 3.83-4.06 (2H), 4.79 (1H) ppm.

Preparation of the building blocks having general formula A" with 2-oxazolidinone auxiliary group

Starting products

A) 2,2-Dimethyl-3-oxopentanal

Aa) 4-(2-Methylprop-1-enyl)morpholine

In a 250 mL three-neck round-bottom flask, 43.6 g of morpholine are placed. While cooling in an ice bath, 46 mL of isobutyraldehyde are added dropwise at a temperature of 5°C within 20 minutes. A strong increase in temperature was observed (strongly exothermic reaction). After completion of the addition, the batch is refluxed for 4 hours through a water separator. The volume of the water separator is filled with isobutyraldehyde. Thus 7.5 mL of H_2O are separated. After completion of the reaction, the reaction mixture is distilled in vacuum.
Oil bath temperature: 85°C-90°C
Main run m = 58.37 g, 82.03%
Boiling point: 59°C at 11 mbar
Yield: 58.37 g, 82.03 % Aa)

A) 2,2-Dimethyl-3-oxopentanal

In a 1000 mL three-neck round-bottom flask, a solution of 77.14 g of propionic acid chloride in 200 mL ether p.a. is placed. Cooling in an ice bath, a solution of 117.73 g of the compound obtained under Aa) in 200 mL of ether p.a. is added dropwise in 30 minutes at a reaction temperature of 6°C. A white precipitate is formed. After completion of the addition, the batch is boiled under reflux for 5 hours and then stirred overnight at room temperature. The obtained white precipitate, which is sensitive to moisture, is filtered off under suction, washed with ether and dried in the vacuum of an oil pump.
Crude product: m = 65.26 g hydrochloride
A post-precipitation is observed in the filtrate.
Crude product m = 35.49 g, total: m = 100.75 g.
The 100.75 g of hydrochloride are dissolved in 150 mL of H_2O. Then the water phase is adjusted to pH 0.5 with $NaHCO_3$ and extracted with ether 4 times using 150 mL each time. The organic phase is washed once with brine and then dried over Na_2SO_4. The ether is

distilled off at normal pressure and the residue is distilled in vacuum through a small Vigreux column (6 theoretical plates).
Main run: m = 29.65 g, 27.75%
Boiling point: 62°C for 15 mbar
Yield: 29.65 g, 27.75% A)

B) 2,2-Dimethyl-3-oxobutanal
The procedure is analogous to A).
Batch: 58.37 g = 413.36 mmole of Aa), M = 141.21 g/mole
100 mL of diethyl ether, p.a.
32.45 g = 413.38 mmole of acetyl chloride,
M = 078.5 g/mole = 1.104 g/mL
100 mL of diethyl ether, p.a.
stirred over the weekend at room temperature.
The crude product m = 72.07 g hydrochloride
For work-up, see Ab)
Oil bath temperature: 75°C to 80°C
Main run: m = 18.75 g, 39.74%
Boiling point: 50°C at 11 mbar
Yield: m = 18.7 g, 39.6% B)

C) 1-(1-Oxopropyl)cyclobutanecarbaldehyde
Ca) 1,1-Cyclobutanedimethanol
To a solution of 20 g (100 mmole) of 1,1-cyclobutanedicarboxylic acid diethyl ester in 200 mL of absolute tetrahydrofuran, 170 mL of a 1.2 molar solution of diisobutylaluminum hydride are added dropwise at 0°C. The mixture is stirred for another hour at 0°C and then 30 mL of water are added. It is filtered through Celite. The filtrate is dried with sodium sulfate and evaporated in vacuum. The obtained crude product (9.9 g) is used in the next step without purification.

Cb) 1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutanemethanol
To a suspension of 3.4 g of sodium hydride (60% in oil, 85 mmole) in 35 mL of absolute tetrahydrofuran, a solution of 9.9 g Ca (85 mmole) in 100 mL of absolute tetrahydrofuran

are added at 0°C. Stirring is continued for 30 minutes and then a solution of 12.8 g of *tert.*-butyldimethylsilyl chloride (85 mmole) in 50 mL of tetrahydrofuran is added. The mixture is stirred for another hour at 25°C and then the reaction mixture is poured into saturated aqueous sodium hydrogen carbonate solution. It is extracted with ethyl acetate. The organic phase is washed with saturated sodium chloride solution and dried over sodium sulfate. After removal of the solvent in vacuum, the obtained crude product is purified by column chromatography on silica gel with a mixture of hexane/ethyl acetate. Thus, 13.5 g (69%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.04 (6H), 0.90 (9H), 1.70-2.00 (6H), 3.70 (4H) ppm.

Cc) 1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutanecarbaldehyde

Oxalyl chloride, 8 mL, is dissolved in 100 mL of dichloromethane. It is cooled to -78°C and 13 mL of dimethylsulfoxide are added. Stirring is continued for 3 minutes and then a solution of 13.5 g of Cb) (58.6 mmole) in 80 mL of dichloromethane are added. After another 15 minutes of stirring, 58 mL of triethylamine are added dropwise. Then the mixture is allowed to warm to 0°C. Then the reaction mixture is poured into saturated sodium hydrogen carbonate solution. It is extracted with dichloromethane, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After chromatography of the crude product on silica gel with a mixture of hexane/ethyl acetate, 7.7 g (58%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.03 (6H), 0.90 (9H), 1.85-2.00 (4H), 2.20-2.30 (2H), 3.83 (2H), 9.70 (1H) ppm.

Cd) 1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]-α-ethylcyclobutanemethanol

A solution of 7.7 g (33.7 mmole) of the compound described under Cc) in 80 mL of tetrahydrofuran is added dropwise at 0°C to 20 mL of a 2 molar solution of ethylmagnesium chloride (40 mmole) in tetrahydrofuran . Stirring is continued for 30 minutes at 0°C and the reaction mixture is then poured into saturated ammonium chloride solution. Extraction is done with ethyl acetate. The organic phase is washed with saturated sodium chloride solution and dried over sodium sulfate. After removal of the solvent, the obtained product is purified by column chromatography on silica gel. Thus, 7.93 g (91.5%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.09 s (6H), 0.90 s (9H), 1.05 (3H), 1.30-1.50 (3H), 1.70-1.90 (4H), 2.09 (1H), 3.19 (1H), 3.46 (1H), 3.72 (1H), 3.85 (1H) ppm.

Ce) 1-[1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobut-1-yl]-1-propanone

To 3.76 mL (43.8 mmole) of oxalyl chloride in 80 mL of dichloromethane, 6 mL (85.7 mmole) dimethylsulfoxide are added at -78°C. Stirring is continued for 3 minutes and then a solution of 7.93 g (30.7 mmole) of the compound described under Cd) in 80 mL of dichloromethane is added. Stirring is continued for another 15 minutes at -78°C. Then a mixture of 19 mL (136 mmole) of triethylamine and 40 mL of dichloromethane is added dropwise. The mixture is allowed to heat up to -25°C and is stirred at this temperature for 30 minutes. Then the reaction mixture is poured into saturated, ice-cold sodium hydrogen carbonate solution. Extraction is done with dichloromethane. The organic phase is washed with saturated sodium chloride solution and dried over sodium sulfate. After removal of the solvent, the obtained crude product is filtered through silica gel. Thus, 7.87 g (100%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.05 (6H), 0.88 (9H), 1.04 (3H), 1.82-1.95 (4H), 2.33-2.47 (2H), 2.45-2.54 (2H), 3.81 (2H) ppm.

Cf) 1-[1-(Hydroxymethyl)cyclobut-1-yl]-1-propanone

The compound described under Ce), 7.87 g (30.7 mmole), is dissolved in 100 mL of tetrahydrofuran. Then 15 mL of a 1 molar solution of tetrabutylammonium fluoride is added and the mixture is stirred for 12 hours at 25°C. Then the reaction mixture is poured into saturated sodium hydrogen carbonate solution. Extraction is done with ethyl acetate. The organic phase is washed with saturated sodium chloride solution and dried over sodium sulfate. After removal of the solvent, the obtained crude product is purified by column chromatography on silica gel. Thus, 3.19 g (73.4%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$: δ = 1.07 (3H), 1.86-2.08 (4H), 2.32-2.40 (2H), 2.55-2.65 (2H), 3.88 (2H) ppm.

C) 1-(1-Oxopropyl)cyclobutanecarbaldehyde

Analogous to Example Ce), starting from 3.19 g (22.4 mmole) of the compound described under Cf), 3.14 g (100%) of the compound in the title are obtained by oxidation.

^{1}H-NMR ($CDCl_3$): δ = 1.07 (3H), 1.85-2.00 (2H), 2.40-2.53 (6H), 9.70 (1H) ppm.

Example 1:

(*R*-4,4-Dimethyl-3-[3-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-5-oxo-heptanoic acid

To a solution of 190 mg of the silyl ether described under Example 1c) in 2.5 mL of a mixture of tetrahydrofuran and water in the ratio of 4:1, 0.17 mL of 30% hydrogen peroxide solution are added at 0°C. After 5 minutes of stirring, a solution of 15.8 mg of lithium hydroxide in 0.83 mL of water is added and the reaction mixture is stirred for 3 hours at 25°C. Then a solution of 208 mg of sodium sulfite in 1.24 mL of water is added and extraction is done with 10 mL of methylene chloride. The aqueous phase is adjusted to pH = 1 with 5 N hydrochloric acid and extracted three times using 10 mL of ethyl acetate each time. After drying over sodium sulfate and filtration, it is evaporated in vacuum. In addition, the above methylene chloride phase is washed with 5 N hydrochloric acid and then this aqueous phase is extracted three times using 10 mL of ethyl acetate each time.

After drying over sodium sulfate and filtration, the mixture is evaporated in vacuum and an additional amount of crude product is obtained. The combined residues thus obtained are purified by chromatography on silica gel. With hexane/0-50% ethyl acetate, in addition to 70 mg of (4*R*,5*S*)-4-methyl-5-phenyloxazolidin-2-one, 93 mg of the compound in the title are obtained as a colorless oil. $[\alpha]_D$ = +15.5° ($CHCl_3$)

^{1}H-NMR ($CDCl_3$): d = 0.03-0.08 (6H), 0.86 (9H), 1.01 (3H), 1.10 (3H), 1.15 (3H), 2.35 (1H), 2.4-2.7 (3H), 4.48 (1H) ppm.

1a) (4*R*,5*S*)-3-(Bromoacetyl)-4-methyl-5-phenyloxazolidin-2-one

To a solution of 30.1 g of (4*R*,5*S*)-4-methyl-5-phenyloxazolidin-2-one in 500 mL of tetrahydrofuran, 117 mL of a 1.6 molar solution of butyllithium in hexane are added within 30 minutes at -70°C under nitrogen. Then a solution of 26.8 g of bromoacetyl chloride in 250 mL of tetrahydrofuran is added dropwise, so that the temperature does not exceed -65°C. After stirring for 1.75 hours at -70°C, a saturated ammonium chloride solution is added, followed by 60 mL of a saturated sodium hydrogen carbonate solution and the mixture is allowed to reach a temperature of 25°C. After separation of the phases, the aqueous phase is extracted twice using 100 mL of ether each time. The combined organic phases are washed with half-concentrated sodium chloride solution, dried over sodium sulfate and, after

filtration, evaporated in vacuum. The residue thus obtained is purified by chromatography on silica gel. Using hexane/0-50% ether, 34.8 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.95 (3H), 4.57 (2H), 4.80 (2H), 5.76 (2H), 7.2-7.5 (5H) ppm.

1b) [4*R*-[3(*R**),4α,5α]]-3-[4,4-Dimethyl-1,5-dioxo-3-hydroxyheptyl]-4-methyl-5-phenyloxazolidin-2-one

To a suspension of 5.0 g of anhydrous chromium(II) chloride in 60 mL of tetrahydrofuran, 218 mg of lithium iodide are added under argon. Then a mixture of 2.09 g of 2,2-dimethyl-3-oxo-pentanal, which is known from the literature (see under "Starting Products" Ab) and 5.34 g of the bromine compound prepared above is added in 10 mL of tetrahydrofuran. After 2 hours of reaction time, 30 mL of saturated sodium chloride solution is added and the mixture is stirred for 15 minutes. The aqueous phase is extracted three times using 200 mL of ether each time. The combined organic phases are washed with half-concentrated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum after filtration. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-30% ethyl acetate, 1.55 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.92 (3H), 1.06 (3H), 1.18 (3H), 1.23 (3H), 2.58 (2H), 3.07 (2H), 3.28 (1H), 4.35 (1H), 4.79 (1H), 5.70 (2H), 7.2-7.5 (5H) ppm.

1c) [4*R*-[3(*R**),4α,5α]]-3-[4,4-Dimethyl-3-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-1,5-dioxoheptyl]-4-methyl-5-phenyloxazolidin-2-one

To a solution of 347 mg of the alcohol prepared above in 3 mL of methylene chloride, 150 mg of 2,6-lutidine are added under argon at -70°C. After 5 minutes of stirring, 344 mg of tert.-butyldimethylsilyltrifluoromethanesulfonate are added and the mixture is stirred for another 45 minutes at -70°C. Then 1 mL of saturated sodium chloride solution is added and the temperature is allowed to rise to 25°C. Then the mixture is diluted with ether and the organic phase is washed with saturated sodium chloride solution. After drying over sodium sulfate and filtration, it is evaporated in vacuum. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-30% ethyl acetate, 190 mg of the compound in the title are obtained as a colorless crystalline compound with a melting point of 111-112°C.

^{1}H-NMR ($CDCl_3$): δ = 0.01-0.12 (6H), 0.86 (9H), 0.90 (3H), 1.00 (3H), 1.13 (3H), 1.17 (3H), 2.56 (2H), 3.05 (2H), 4.65-4.80 (2H), 5.68 (1H), 7.2-7.5 (5H) ppm.

Example 2

(*S*)-4,4-Dimethyl-3-[3-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-5-oxo-heptanoic acid

The compound is prepared analogously to Example 1. (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one serves as starting product. The NMR is superimposable with that of Example 1.
$[\alpha]_D$ = -15.7° ($CHCl_3$)

2a) (4*S*,5*R*)-3-(Bromoacetyl)-4-methyl-5-phenyloxazolidin-2-one

The preparation is done analogously to Example 1a) starting from (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one. The NMR is superimposable to that in 1a).

Example 3

(*S*)-3-3-[[Dimethyl(1,1-dimethyl)silyl]oxy]-3-[1,(1-oxopropyl)cyclobut-1-yl]propanoic acid

Analogously to Example 1, starting from 2.79 g (5.9 mmole) of the compound described under 3b), 1.49 g (80%) of the compound in the title and 941 mg recovered (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one are obtained. The compound in the title and the recovered chiral auxiliary can be separated by chromatography (analogous to Example 1) but also by fractional crystallization and then purified further by chromatography if desired.
^{1}H-NMR ($CDCl_3$): δ = 0.09 (3H), 0.19 (3H), 0.90 (9H), 1.08 (3H), 1.70-2.00 (3H), 2.20-2.40 (4H), 2.47 (1H), 2.50-2.70 (2H), 4.45 (1H) ppm.

3a) [4*S*-[3(*R**),4α,5α]]-3-[3-Hydroxy-1-oxo-3-[1-(1-oxopropyl)cyclobut-1-yl]propyl]-4-methyl-5-phenyloxazolidin-2-one

Analogously to Example 1b), starting from 3.14 g (22.4 mmole) of the compound described under C), 9.7 g (78.8 mmole) of anhydrous chromium(II) chloride, 9.69 g (32.5 mmole) of 2a) and 300 mg (2.2 mmole) of anhydrous lithium iodide in tetrahydrofuran, 3.0 g (37.4%) of the compound in the title are obtained after column chromatography on silica gel as a colorless oil.
^{1}H-NMR ($CDCl_3$): δ = 0.93 (3H), 1.10 (3H), 1.80-2.03 (2H), 2.10-2.21 (1H), 2.26-2.35 (3H), 2.54-2.70 (2H), 3.03-3.08 (2H), 3.34 (1H), 4.39 (1H), 4.74-4.85 (1H), 5.69 (1H), 7.27-7.34 (2H), 7.36-7.49 (3H) ppm.

3b) [4*S*-[3(*R**),4α,5α]]-3-[3-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-1-oxo-3-[1-(1-oxopropyl)cyclobut-1-yl]propyl]-4-methyl-5-phenyloxazolidin-2-one

Analogously to Example 1c), starting from 3.0 g (8.35 mmole) of the compound described in Example 3a), tert.-butyldimethylsilyltrifluoromethanesulfonate and 2,6-lutidine, after recrystallization from diisopropyl ether, 2.79 g (70.6%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.10 (3H), 0.21 (3H), 0.92 (3H), 0.95 (9H), 1.10 (3H), 1.70-1.92 (2H), 2.02-2.16 (1H), 2.20-2.40 (3H), 2.50-2.72 (2H), 2.98-3.10 (2H), 4.63-4.75 (1H), 5.69 (1H), 7.28-7.35 (2H), 7.36-7.48 (3H) ppm.

Example 4

(*R*)-3-[3-[[Dimethyl(1,1-dimethyl)silyl]oxy]-3-[1-(1-oxopropyl)cyclobut-1-yl]propanoic acid

The compound is prepared analogously to Example 3. (4*R*,5*S*)-3-(bromoacetyl)-4-methyl-5-phenyloxazolidin-2-one serves as starting material.

The NMR spectrum is superimposable to that in Example 3.

By choosing the stereochemistry at C4 and C5 of the chiral auxiliary, 4-methyl-5-phenyl-2-oxazolidone, one can control the stereochemistry in position 3.

The structure of the intermediate 1b) was proven by x-ray structural analysis.

Examples for the preparation of building block C

Example 1

(*S*)-Dihydro-3-hydroxy-2(3*H*)-furanone

10 g of L-(-)-malic acid in 45 mL of trifluoroacetic anhydride are stirred for 2 hours at 25°C. Then it is evaporated in vacuum, 7 mL of methanol are added to the residue and the mixture is stirred for another 12 hours. Then it is evaporated in vacuum. The obtained residue is dissolved in 150 mL of absolute tetrahydrofuran. It is cooled to 0°C and 150 mL of borane/tetrahydrofuran complex are added and the mixture is stirred for 2.5 hours at 0°C. After that, 150 mL of methanol are added. Stirring is continued for 1 hour at room temperature, followed by evaporation in vacuum. The obtained crude product is dissolved in 80 mL of toluene. Then 5 g of Dowex® (activated, acidic) are added followed by boiling for

one hour under reflux. Then the Dowex® is filtered off and the filtrate is evaporated in vacuum. The obtained crude product (7.61 g; 99.9%) is used in the next step without purification.

Example 2

(*S*)-Dihydro-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2(3*H*)-furanone

To a solution of 7.61 g of the substance described in Example 1 and 10 g of imidazole in 100 mL of *N,N*-dimethylformamide, 24 mL of *tert.*-butyldiphenylsilyl chloride are added. The reaction mixture is stirred for two hours at 25°C and then poured into ice-cold saturated sodium hydrogen carbonate solution. After extraction with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After column chromatography of the crude product on silica gel with a mixture of hexane/ethyl acetate, 13.4 g (52.8%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 7.72 (2H), 7.70 (2H), 7.40-7.50 (6H), 4.30-4.42 (2H), 4.01 (1H), 2.10-2.30 (2H), 1.11 (9H) ppm.

Example 3

(2RS,3*S*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]tetrahydro-2-furanol

To a solution of 13.4 g of the substance described in Example 2 in 150 mL of absolute tetrahydrofuran, 80 mL of a 1 molar solution of diisobutylaluminum hydride in hexane are added at -78°C. The mixture is stirred for 45 minutes at -78°C and then quenched with water. After extraction with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. Thus, 13.46 g (99.4%) of the compound in the title are obtained, which is used in the next step without purification.

Example 4

(2RS,3*S*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1,4-pentanediol

To 20 mL of a 3 molar solution of methylmagnesium chloride in tetrahydrofuran, at 0°C, a solution of 13.46 g of the substance described in Example 3 in 150 mL of absolute tetrahydrofuran are added dropwise. The mixture is stirred for another hour at 0°C and then poured into saturated aqueous ammonium chloride solution. After extraction with ethyl

acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After column chromatography of the crude product on silica gel with a mixture of hexane/ethyl acetate, 11.42 g (81.6%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 7.65-7.75 (4H), 7.40-7.55 (6H), 5.20 (1H), 4.30 (2H), 3.70 (1H), 1.80 (2H), 1.05 (9H) ppm.

Example 5

(2RS,3*S*)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-pentanol

To a solution of 11.42 g of the substance described in Example 4 and 3.25 g of 1*H*-imidazole in 120 mL of *N,N*-dimethylformamide, 4.9 g of *tert.*-butyldimethylsilyl chloride are added. Stirring is continued for 2 hours at 25°C and then the reaction mixture is poured into ice-cold saturated sodium hydrogen carbonate solution. After extraction with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After column chromatography of the crude product on silica gel with a mixture of hexane/ethyl acetate, 10.64 g (70.5%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 7.60-7.70 (4H), 7.30-7.45 (6H), 3.70-3.80 (2H), 3.40 (1H), 3.00 (1H), 1.80 (1H), 1.60 (1H), 1.05-1.12 (12H), 0.82 (9H), 0.02 (6H) ppm.

Example 6

(3*S*)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-pentanone

To 7.37 mL of oxalyl chloride in 80 mL of dichloromethane, 13 mL of dimethylsulfoxide are added at -78°C. The mixture is stirred for another 3 minutes and then 10.64 g of the substance described in Example 5 in 100 mL of dichloromethane are added. After another 15 minutes of stirring time, 52 mL of triethylamine are added dropwise. Then the mixture is allowed to heat to 0°C. After that, the reaction mixture is poured onto saturated sodium hydrogen carbonate solution. It is extracted with dichloromethane, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After column chromatography of the crude product on silica gel with a mixture of

hexane/ethyl acetate, 9.3 g (26.5% based on the malic acid used) of the compound in the title are obtained.
^{1}H-NMR ($CDCl_3$): δ = 7.60-7.70 (4H), 7.32-7.50 (6H), 4.25 (1H), 3.72 (1H), 3.58 (1H), 2.05 (3H), 1.90 (1H), 1.75 (1H), 1.13 (9H), 0.89 (9H), 0.01 (6H) ppm.

Example 7

(*R*)-Dihydro-3-hydroxy-2(3*H*)-furanone

D-(+)-Malic acid, 10 g is reacted analogously to Example 1. Thus, 7.26 g of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 1.

Example 8

(*R*)-Dihydro-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2(3*H*)-furanone

Analogously to Example 2, starting from 7.26 g of the substance described in Example 7, 12.9 g of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 2.

Example 9

(2RS,3*R*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]tetrahydro-2-furanol

Analogously to Example 3, starting from 12.9 g of the substance described in Example 8, 12.95 g of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 3.

Example 10

(2RS,3*R*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1,4-pentanediol

Analogously to Example 4, starting from 12.95 g of the substance described in Example 9, 11 g of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 4.

Example 11

(2RS,3*R*)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-pentanol

Analogously to Example 5, starting from 11 g of the substance described in Example 10, 10.11 g of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 5.

Example 12

(*R*)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-pentanone

Analogously to Example 6, starting from 10.11 g of the substance described in Example 11, 8.85 g of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 6.

Example 13

(3RS)-Dihydro-3-hydroxy-2(3*H*)-furanone

5 g of racemic malic acid are reacted analogously to Example 1. Thus, 3.68 g of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 1.

Example 14

(3RS)-Dihydro-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2(3*H*)-furanone

Analogously to Example 2, starting from 3.68 g of the substance described in Example 13, 6.5 g of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 2.

Example 15

(2RS,3RS)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]tetrahydro-2-furanol

Analogously to Example 3, starting from 6.5 g of the substance described in Example 14, 6.51 g of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 15.

Example 16

(2RS,3RS)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1,4-pentanediol

Analogously to Example 4, starting from 6.51 g of the substance described in Example 15, 5.5 g of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 4.

Example 17

(2RS,3RS)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]-oxy]-2-pentanol

Analogously to Example 5, starting from 5.5 g of the substance described in Example 16, 5.05 g of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 5.

Example 18

(3RS)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-pentanone

Analogously to Example 6, starting from 5.05 g of the substance described in Example 17, 4.3 g of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 6.

Example 19

(E,3S)-1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene

The solution of 6.82 g of diethyl(2-methylthiazol-4-yl)methane phosphonate in 300 mL of anhydrous tetrahydrofuran is cooled under a dry argon atmosphere to -5°C, treated with 16.2 mL of a 1.6 molar solution of n-butyllithium in n-hexane, is allowed to warm to 23°C and is stirred for 2 hours. Then it is cooled to -78°C, and a solution of 6.44 g (13.68 mmole) of the compound prepared according to Example 16 in 150 mL of tetrahydrofuran is added dropwise, followed by allowing the mixture to warm up to 23°C and stirring for 16 hours. It is poured into saturated ammonium chloride solution, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane

and ethyl acetate. Thus, 6.46 g (11.4 mmole, 83%; yield is based on the malic acid used: 22%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.04 (6H), 0.83 (9H), 1.10 (9H), 1.79 (1H), 1.90 (1H), 1.97 (3H), 2.51 (3H), 3.51 (2H), 4.38 (1H), 6.22 (1H), 6.74 (1H), 7.23-7.47 (6H), 7.63 (2H), 7.70 (2H) ppm.

Example 20

(E,3S)-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-ol

The solution of 4.79 g (8.46 mmole) of the compound prepared according to Example 19 in 48 mL of tetrahydrofuran is treated with 48 mL of a 65:35:10 mixture of glacial acetic acid/water/tetrahydrofuran and stirred for 2.5 days at 23°C. It is poured into saturated sodium carbonate solution, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 3.42 g (7.57 mmole, 90%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.10 (9H), 1.53 (1H), 1.81 (2H), 1.96 (3H), 2.71 (3H), 3.59 (2H), 4.41 (1H), 6.38 (1H), 6.78 (1H), 7.26-7.49 (6H), 7.65 (2H), 7.72 (2H) ppm.

Example 21

(E,3S)-1-Bromo-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene

The solution of 378 mg (0.84 mmole) of the compound prepared according to Example 20 in 9 mL of dichloromethane is treated at 0°C under a dry argon atmosphere with 90 μL of pyridine, 439 mg of triphenylphosphine, 556 mg of tetrabromomethane and is stirred for 1 hour at 0°C. The solution is chromatographed on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 362 mg (0.70 mmole, 84%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.09 (9H), 1.95 (3H), 2.01-2.23 (2H), 2.71 (3H), 3.15-3.35 (2H), 4.35 (1H), 6.30 (1H), 6.79 (1H), 7.25-7.49 (6H), 7.63 (2H), 7.69 (2H) ppm.

Example 22

(E,3S)-1-Iodine-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene

The solution of 8.41 g of triphenylphosphine in 120 mL of dichloromethane is treated at 23°C under a dry argon atmosphere with 2.19 g of imidazole, 8.14 g of iodine, the solution of 12.2 g (27.0 mmole) of the compound prepared according to Example 20 in 30 mL of dichloromethane is added dropwise and the mixture is stirred for 0.5 hours. The solution is chromatographed on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 12.15 g (21.6 mmole, 80%) of the compound in the title are isolated as a colorless oil.
^{1}H-NMR ($CDCl_3$): δ = 1.08 (9H), 1.96 (3H), 2.10 (2H), 2.70 (3H), 2.87-3.08 (2H), 4.24 (1H), 6.32 (1H), 6.79 (1H), 7.28-7.48 (6H), 7.60-7.72 (4H) ppm.

Example 23

(5E,3S)-[3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-yl-triphenylphosphonium iodide

The suspension of 12.55 g (22.3 mmole) of the compound prepared according to Example 22, 85 g of triphenylphosphine and 11.6 mL of N-ethyldiisopropylamine is stirred under a dry argon atmosphere for 16 hours at 80°C. After cooling, diethyl ether is added, the mixture is filtered and the residue is washed several times with diethyl ether and is recrystallized from ethyl acetate. Thus, 15.7 g (19.1 mmole, 74%) of the compound in the title are isolated as crystalline solid.
^{1}H-NMR ($CDCl_3$): δ = 1.07 (9H), 1.68-1.92 (2H), 1.98 (3H), 2.70 (3H), 2.93 (1H), 3.30 (1H), 4.53 (1H), 6.62 (1H), 7.03 (1H), 7.23-7.47 (6H), 7.48-7.72 (16H), 7.73-7.85 (3H) ppm.

Example 24

(E,3R)-1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene

Analogously to Example 19, starting from 8.85 g of the compound described under Example 12, 8.56 g (80%) of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 19.

Example 25

(E,3R)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-ol

Analogously to Example 20, starting from 8.56 g of the compound described under Example 24, 6.25 g (92%) of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 20.

Example 26

(E,3R)-1-Iodine-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene

Analogously to Example 22, starting from 6.25 g of the compound described under Example 25, 6.22 g (80%) of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 22.

Example 27

(5E,3R)-[3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-yl]-triphenylphosphonium iodide

Analogously to Example 23, starting from 6.22 g of the compound described under Example 26, 7.36 g (70%) of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 23.

Example 28

(E,3RS)-1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]-oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene

Analogously to Example 19, starting from 4.3 g of the compound described under Example 18, 4.52 g (87%) of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 19.

Example 29

(E,3RS)-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-ol

Analogously to Example 20, starting from 4.52 g of the compound described under Example 28, 3.16 g (88%) of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 20.

Example 30

(E,3RS)-1-Iodine-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene

Analogously to Example 22, starting from 3.16 g of the compound described under Example 25, 3.34 g (85%) of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 22.

Example 31

(5E,3RS)-[3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-yl]-triphenylphosphonium iodide

Analogously to Example 23, starting from 3.34 g of the compound described under Example 26, 4.35 g (77%) of the compound in the title are obtained. The ^{1}H-NMR spectrum is superimposable with 23.

Example 32

(E,3S)-1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-pyridyl)-pent-4-ene

In analogy to Example 19, 2 g (4.23 mmole) of the compound prepared according to Example 6 is reacted using diethyl(2-pyridyl)methanephosphonate and after work-up and purification, 2 g (3.68 mmole, 87%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.06 (6H), 0.80 (9H), 1.09 (9H), 1.81 (1H), 1.90 (1H), 2.00 (3H), 3.53 (2H), 4.40 (1H), 6.22 (1H), 6.99 (1H), 7.06 (1H), 7.25-7.45 (6H), 7.58 (1H), 7.65-7.77 (4H), 8.58 (1H) ppm.

Example 33

(E,3S)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-pyridyl)-pent-4-en-1-ol

Analogously to Example 20, 2 g (3.68 mmole) of the compound prepared according to Example 32 are reacted with a 65:35:10 mixture of glacial acetic acid/water/tetrahydrofuran. After purification, 1.38 g (3.20 mmole, 87%) of the compound in the title are obtained.
^{1}H-NMR ($CDCl_3$): δ = 1.12 (9H), 1.85 (2H), 2.00 (3H), 3.62 (2H), 4.45 (1H), 6.44 (1H), 7.03 (1H), 7.08 (1H), 7.25-7.48 (6H), 7.59 (1H), 7.65-7.77 (4H), 8.58 (1H) ppm.

Example 34

(Z,3S)-1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(3-pyridyl)-pent-4-ene (A) and (E,3S)-1-[[dimethyl(1,1-dimethylethyl)silyl]-oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(3-pyridyl)-pent-4-ene(B)

In analogy to Example 19, 4.8 g (10.2 mmole) of the compound prepared according to Example 6 is reacted using diethyl(3-pyridyl)methanephosphonate and, after work-up and purification, 448 mg (0.82 mmole, 8%) of compound A in the title, as well as 3.5 g (6.41 mmole, 63%) of compound B in the title are obtained, each as a colorless oil.
^{1}H-NMR ($CDCl_3$) of A: δ = -0.06 (6H), 0.81 (9H), 1.01 (9H), 1.75 (1H), 1.97 (4H), 3.48 (2H), 4.83 (1H), 6.11 (1H), 6.97 (1H), 7.11-7.30 (5H), 7.30-7.39 (2H), 7.39-7.50 (4H), 8.08 (1H), 8.33 (1H) ppm.
^{1}H-NMR ($CDCl_3$) of B: δ = -0.01 (6H), 0.85 (9H), 1.11 (9H), 1.78 (3H), 1.83 (1H), 1.97 (1H), 3.58 (2H), 4.42 (1H), 6.03 (1H), 7.21 (1H), 7.28-7.50 (7H), 7.62-7.75 (4H), 8.29 (1H), 8.41 (1H) ppm.

Example 35

(E,3S)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(3-pyridyl)-pent-4-en-1-ol

Analogously to Example 20, 3.5 g (6.41 mmole) of the compound prepared according to Example 34B are reacted with a 65:35:10 mixture of glacial acetic acid/water/tetrahydrofuran. After purification, 2.1 g (4.86 mmole, 76%) are obtained.
^{1}H-NMR ($CDCl_3$): δ = 1.12 (9H), 1.75 (3H), 1.88 (2H), 3.65 (2H), 4.45 (1H), 6.25 (1H), 7.21 (1H), 7.28-7.50 (7H), 7.60-7.75 (4H), 8.30 (1H), 8.44 (1H) ppm.

Example 36

Analogously to Example 22, starting from the compound described in Example 35, 1.98 g (75%) of the compound in the title are obtained [there is no title compound in the German text - T.]

^{1}H-NMR ($CDCl_3$): δ = 1.11 (9H), 1.78 (3H), 2.17 (2H), 3.03 (2H), 4.29 (1H), 6.19 (1H), 7.22 (1H), 7.30-7.50 (7H), 7.63-7.75 (4H), 8.32 (1H), 8.44 (1H) ppm.

Example 37

Analogously to Example 23, starting from 1.98 g of the compound described in Example 36, 2.35 g (80%) of the compound in the title are obtained [there is no title compound in the German text - T.]

^{1}H-NMR ($CDCl_3$): δ = 1.08 (9H), 1.80 (3H), 3.27 (1H), 3.56 (1H), 4.66 (1H), 6.52 (1H), 7.25-7.90 (27H), 8.35 (1H), 8.46 (1H) ppm.

Example 38

(Z,3S)-1-[[Dimethyl(1,1-dimethylethyl)silyl]oxyl-3-[[(1,1-dimethylethyl)diphenylsilyl]oxyl-4-methyl-5-(4-pyridyl)-pent-4-ene (A) and (E,3S)-1-[[dimethyl(1,1-dimethylethyl)silyl]-oxyl-3-[[(1,1-dimethylethyl)diphenylsilyl]oxyl-4-methyl-5-(4-pyridyl)-pent-4-ene(B)

In analogy to Example 19, 4.59 g (9.75 mmole) of the compound prepared according to Example 6 are reacted using diethyl(4-pyridyl)methanephosphonate and, after work-up and purification, 605 mg (1.11 mmole, 11%) of compound A in the title as well as 4.34 g (7.95 mmole, 82%) of compound B in the title are obtained, each as a colorless oil.

^{1}H-NMR ($CDCl_3$) of A: δ = -0.05 (6H), 0.82 (9H), 1.02 (9H), 1.78 (1H), 1.96 (3H), 3.48 (2H), 4.92 (1H), 6.08 (1H), 6.73 (2H), 7.20-7.30 (4H), 7.32-7.40 (2H), 7.41-7.49 (4H), 8.30 (2H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = -0.04 (6H), 0.80 (9H), 1.08 (9H), 1.78 (3H), 1.91 (1H), 3.55 (2H), 4.39 (1H), 6.02 (1H), 6.93 (2H), 7.26-7.48 (6H), 7.60-7.72 (4H), 8.50 (2H) ppm.

Example 39

(E,3S)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxyl-4-methyl-5-(4-pyridyl)-pent-4-en-1-ol

Analogously to Example 20, 4.34 g (7.95 mmole) of the compound prepared in Example 38B are reacted with a 65:35:10 mixture of glacial acetic acid/water/tetrahydrofuran. After purification, 2.92 g (6.76 mmole, 85%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 1.12 (9H), 1.78 (3H), 1.87 (2H), 3.65 (2H), 4.42 (1H), 6.26 (1H), 6.97 (2H), 7.26-7.48 (6H), 7.60-7.72 (4H), 8.52 (2H) ppm.

Example 40

Analogously to Example 22, starting from 2.92 g (6.76 mmole) of the compound described in Example 39, 2.82 g (77%) of the compound in the title are obtained [there is no title compound in the German text - T.]

^{1}H-NMR ($CDCl_3$): δ = 1.08 (6H), 1.78 (3H), 2.15 (2H), 3.00 (2H), 4.26 (1H), 6.17 (1H), 6.95 (2H), 7.30-7.50 (6H), 7.60-7.70 (4H), 8.50 (2H) ppm.

Example 41

Analogously to Example 23, starting from 2.82 g (5.21 mmole) of the compound described in Example 40, 3.27 g (4.06 mmole, 78%) of the compound in the title are obtained [there is no title compound in the German text - T.]

^{1}H-NMR ($CDCl_3$): δ = 1.09 (6H), 1.82 (3H), 3.15 (1H), 3.50 (1H), 4.65 (1H), 6.53 (1H), 7.05 (2H), 7.25-7.48 (6H), 7.50-7.70 (4H), 8.50 (2H) ppm.

Preparation of the epothilone derivatives having general formula I:

Example 1

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethylcyclohexadec-13-ene-2,6-dione

Example 1a

(3S)-1-Oxa-2-oxo-3-(tetrahydropyran-2(RS)-yloxy)-4,4-dimethylcyclopentane

The solution of 74.1 g (569 mmole) of D-(-)-pantolactone in 1 L anhydrous dichloromethane is treated in a dry argon atmosphere with 102 mL of 3,4-dihydro-2H-pyrane, 2 g of p-toluenesulfonic acid pyridinium salt and the mixture is stirred for 16 hours at 23°C. It is poured into a saturated sodium hydrogen carbonate solution, the organic phase is separated and dried over sodium sulfate. After filtration and removal of the solvent, the residue is chromatographed on approximately 5 kg of a fine silica gel with a mixture of n-hexane and ethyl acetate. Thus, 119.6 g (558 mmole, 98%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.13 (3H), 1.22 (3H), 1.46-1.91 (6H), 3.50-3.61 (1H), 3.86 (1H), 3.92 (1H), 4.01 (1H), 4.16 (1H), 5.16 (1H) ppm.

Example 1b

(2RS,3S)-1-Oxa-2-hydroxy-3-(tetrahydropyran-2(RS)-yloxy)-4,4-dimethylcyclopentane

The solution of 117.5 g (548 mmole) of the compound prepared according to Example 1a in 2.4 L anhydrous toluene is cooled under a dry argon atmosphere to -70°C and, over a period of 1 hour, 540 mL of a 1.2 molar solution of diisobutylaluminum hydride in toluene are added and the mixture is stirred for another 3 hours at -70°C. The mixture is allowed to warm up to -20°C, then saturated ammonium chloride solution and water are added and the precipitated aluminum salts are removed by filtration through Celite. The filtrate is washed with water and saturated sodium chloride solution and dried over magnesium sulfate. Thus, after filtration and removal of the solvent, 111.4 g (515 mmole, 94%) of the compound in the title are isolated as a colorless oil, which is reacted further without purification.

IR ($CHCl_3$): 3480, 3013, 2950, 2874, 1262, 1133, 1074, 1026 and 808 cm^{-1}.

Example 1c

(3S)-2,2-Dimethyl-3-(tetrahydropyran-2(R)-yloxy)-pent-4-en-1-ol and (3S)-2,2-dimethyl-3-(tetrahydropyran-2(S)-yloxy)-pent-4-en-1-ol

The suspension of 295 g of methyltriphenylphosphonium bromide in 2.5 L anhydrous tetrahydrofuran is treated in a dry argon atmosphere at -60°C with 313 mL of a 2.4 molar solution of n-butyllithium in n-hexane. The mixture is allowed to warm up to 23°C, is stirred for another hour and then cooled to 0°C. Then the solution of 66.2 g (306 mmole) of the compound prepared according to Example 1b in 250 mL of tetrahydrofuran are added to it, the mixture is allowed to warm up to 23°C and is stirred for 18 hours. It is poured into a saturated sodium hydrogen carbonate solution, extracted several times with dichloromethane and the combined organic extracts are dried over sodium sulfate. After filtration and removal of the solvent, the residue is chromatographed on approximately 5 L of fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 36.5 g (170 mmole, 56%) of the nonpolar THP isomer, 14.4 g (67.3 mmole, 22%) of the polar THP isomer of the compound in the title were isolated together with 7.2 g (33.3 mmole, 11%) of the starting material, each as a colorless oil.

^{1}H-NMR ($CDCl_3$), nonpolar isomer: δ = 0.78 (3H), 0.92 (3H), 1.41-1.58 (4H), 1.63-1.87 (2H), 3.18 (1H), 3.41 (1H), 3.48 (1H), 3.68 (1H), 3.94 (1H), 4.00 (1H), 4.43 (1H), 5.19 (1H), 5.27 (1H), 5.75 (1H) ppm.

^{1}H-NMR ($CDCl_3$), polar isomer: δ = 0.83 (3H), 0.93 (3H), 1.42-1.87 (6H), 2.76 (1H), 3.30 (1H), 3.45 (1H), 3.58 (1H), 3.83 (1H), 3.89 (1H), 4.65 (1H), 5.12-5.27 (2H), 5.92 (1H) ppm.

Example 1d

(3S)-1-(tert.-Butyldiphenylsilyloxy)-2,2-dimethylpentane-3-(tetrahydropyran-2-yloxy)-pent-4-ene

The solution of 59.3 g (277 mmole) of the THP isomer mixture prepared according to Example 1c in 1000 mL of anhydrous dimethylformamide is treated in a dry argon atmosphere with 28 g of imidazole, 85 mL of tert.-butyldiphenylchlorosilane and the mixture is stirred for 16 hours at 23°C. It is poured into water, extracted several times with dichloromethane, the combined organic extracts are washed with water and dried over sodium sulfate. After filtration and removal of the solvent, the residue is chromatographed on fine

silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 106.7 g (236 mmole, 85%) of the compound in the title are isolated as a colorless oil.
^{1}H-NMR ($CDCl_3$): δ = 0.89 (3H), 0.99 (3H), 1.08 (9H), 1.34-1.82 (6H), 3.40 (1H), 3.51 (2H), 3.76 (1H), 4.02 (1H), 4.67 (1H), 5.18 (1H), 5.23 (1H), 5.68 (1H), 7.30-7.48 (6H), 7.60-7.73 (4H) ppm.

Example 1e

(3S)-1-(tert.-Butyldiphenylsilyloxy)-2,2-dimethyl-3-(tetrahydropyran-2-yloxy)-pentan-5-ol

The solution of 3.09 g (6.83 mmole) of the compound prepared according to Example 1d in 82 mL of tetrahydrofuran is treated in a dry argon atmosphere at 23°C with 13.1 mL of a 1 molar solution of borane in tetrahydrofuran and the mixture is allowed to react for 1 hour. Then, under cooling with ice, 16.4 mL of a 5% sodium hydroxide solution as well as 8.2 mL of a 30% hydrogen peroxide solution are added and the mixture is stirred for another 30 minutes. It is poured into water, extracted several times with ethyl acetate, the combined organic extracts are washed with water, saturated sodium chloride solution and dried over magnesium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 1.78 g (3.78 mmole, 55%) of the compound in the title are isolated as a chromatographically separable mixture of the two THP epimers together with 0.44 g (1.14 mmole, 17%) of the compound in the title from Example 6, each as a colorless oil.
^{1}H-NMR ($CDCl_3$), nonpolar THP isomer: δ = 0.80 (3H), 0.88 (3H), 1.10 (9H), 1.18-1.80 (9H), 3.27 (1H), 3.39 (1H), 3.48 (1H), 3.64 (1H), 3.83 (1H), 3.90-4.08 (2H), 4.49 (1H), 7.31-7.50 (6H), 7.58-7.73 (4H) ppm.
^{1}H-NMR ($CDCl_3$), polar THP isomer: δ = 0.89 (3H), 0.98 (3H), 1.08 (9H), 1.36-1.60 (4H), 1.62-1.79 (3H), 1.88 (1H), 2.03 (1H), 3.37 (1H), 3.50 (1H), 3.57 (1H), 3.62-3.83 (4H), 4.70 (1H), 7.30-7.48 (6H), 7.61-7.73 (4H) ppm.

Example 1f

(3S)-1-(tert.-Butyldiphenylsilyloxy)-2,2-dimethyl-3-hydroxypent-4-ene

The solution of 106.7 g (236 mmole) of the compound prepared according to Example 1d in 1.5 L anhydrous ethanol is treated in a dry argon atmosphere with 5.9 g of pyridinium-p-toluenesulfonate and heated for 6 hours at 50°C. After removal of the solvent, the residue is chromatographed on fine silica gel with a mixture of n-hexane and ethyl acetate. Thus, 82.6

g (224 mmole, 95%) of the compound in the title are isolated as a colorless oil, which contains in addition approximately 5 g of ethoxytetrahydropyrane.

^{1}H-NMR ($CDCl_3$) of an analytical sample: δ = 0.89 (6H), 1.08 (9H), 3.45 (1H), 3.49 (1H), 3.58 (1H), 4.09 (1H), 5.21 (1H), 5.33 (1H), 5.93 (1H), 7.34-7.51 (6H), 7.63-7.73 (4H) ppm.

Example 1g

(3S)-1-(tert.-Butyldiphenylsilyloxy)-2,2-dimethylpentane-3,5-diol

The solution of 570 mg (1.55 mmole) of the compound prepared according to Example 1f is reacted in analogy to Example 1e and, after work-up and purification, 410 mg (1.06 mmole, 68%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.82 (3H), 0.93 (3H), 1.08 (9H), 1.56-1.79 (2H), 3.11 (1H), 3.50 (2H), 3.78-3.92 (3H), 4.02 (1H), 7.34-7.51 (6H), 7.61-7.71 (4H) ppm.

Example 1h

4(S)-[2-Methyl-1-(tert.-butyldiphenylsilyloxy)-prop-2-yl]-2,2-dimethyl-[1,3]dioxane

The solution of 100 mg (0.212 mmole) of the compounds prepared according to Example 1e in 2.6 mL of anhydrous acetone is treated under a dry argon atmosphere with 78.9 mg of copper(II) sulfate, a spatula-tip of p-toluenesulfonic acid monohydrate and the mixture is stirred for 16 hours at 23°C. Saturated sodium hydrogen carbonate solution is added, extracted several times with diethyl ether, washed with saturated sodium chloride solution and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 24 mg (56 μmole, 27%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.83 (3H), 0.89 (3H), 1.07 (9H), 1.30 (1H), 1.36 (3H), 1.44 (3H), 1.71 (1H), 3.24 (1H), 3.62 (1H), 3.86 (1H), 3.91-4.03 (2H), 7.31-7.48 (6H), 7.61-7.74 (4H) ppm.

Variant II

The compound prepared according to Example 1g, 320 mg (0.88 mmole), is reacted in analogy to Example 1h, variant I and, after work-up and purification, 234 mg (0.548 mmole, 62%) of the compound in the title are isolated.

Variant III

The solution of 5.60 g (14.5 mmole) of the compound prepared according to Example 1g in 250 mL of anhydrous dichloromethane is treated under a dry argon atmosphere with 10 mL of 2,2-dimethoxypropane, 145 mg of camphor-10-sulfonic acid and the mixture is stirred for 6 hours at 23°C. Then triethylamine is added, the mixture is diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution and dried over sodium sulfate. After filtration and removal of the solvent, the residue is chromatographed on fine silica gel with a mixture of n-hexane and ethyl acetate. Thus, 5.52 g (12.9 mmole, 89%) of the compound in the title are isolated as a colorless oil.

Example 1i

(4S)-4-(2-Methyl-1-hydroxyprop-2-yl)-2,2-dimethyl-[1,3]dioxane

The solution of 5.6 g (13.1 mmole) of the compound prepared according to Example 1h in 75 mL of anhydrous tetrahydrofuran is treated under a dry argon atmosphere with 39 mL of a 1 molar solution of tetrabutylammonium fluoride in tetrahydrofuran and the mixture is heated for 16 hours at 50°C. Saturated sodium hydrogen carbonate solution is added, the mixture is extracted several times with ethyl acetate, washed with saturated sodium chloride solution and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 2.43 g (12.9 mmole, 99%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.87 (3H), 0.90 (3H), 1.35 (1H), 1.37 (3H), 1.43 (3H), 1.77 (1H), 2.93 (1H), 3.36 (1H), 3.53 (1H), 3.79 (1H), 3.87 (1H), 3.96 (1H) ppm.

Example 1k

(4S)-4-(2-Methyl-1-oxoprop-2-yl)-2,2-dimethyl-[1,3]dioxane

The solution of 0.13 mL of oxalyl chloride in 5.7 mL of anhydrous dichloromethane is cooled under a dry argon atmosphere to -70°C, followed by the addition of 0.21 mL of dimethylsulfoxide, and the solution of 200 mg (1.06 mmole) of the compound prepared according to Example 1i in 5.7 mL of anhydrous dichloromethane and the mixture is stirred for 0.5 hours. Then 0.65 mL of triethylamine are added, the mixture is allowed to react for 1 hour at -30°C and n-hexane and saturated sodium hydrogen carbonate solution are added. The organic phase is separated, the aqueous phase is extracted several times more with

n-hexane, the combined organic extracts are washed with water and dried over magnesium sulfate. The residue obtained after filtration and removal of the solvent is reacted further without purification.

Example 1l

(4S)-4-((3RS)-2-Methyl-3-hydroxyhex-2-yl)-2,2-dimethyl-[1,3]dioxane

The solution of 450 mg (2.42 mmole) of the compound prepared according to Example 1k in 7 mL of anhydrous diethyl ether is treated in a dry argon atmosphere at 0°C with 1.21 mL of a 2.4 molar solution of propylmagnesium bromide in diethyl ether; the mixture is allowed to heat up to 23°C and is then stirred for 16 hours. Saturated ammonium chloride solution is added, the organic phase is separated and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 244 mg (1.06 mmole, 44%) of the chromatographically separable 3R- and 3S-epimers of the compound in the title as well as 191 mg of the compound described in the title in Example 1i, are obtained, each as a colorless oil.

^{1}H-NMR ($CDCl_3$) nonpolar isomer: δ = 0.87 (3H), 0.89 (3H), 0.94 (3H), 1.25-1.52 (4H), 1.38 (3H), 1.45 (3H), 1.66 (1H), 1.85 (1H), 3.46 (1H), 3.80-4.02 (4H) ppm.

^{1}H-NMR ($CDCl_3$) polar isomer: δ = 0.73 (3H), 0.92 (3H), 0.95 (3H), 1.19-1.84 (6H), 1.37 (3H), 1.49 (3H), 3.49 (1H), 3.60 (1H), 3.80-4.03 (3H) ppm.

Example 1m

(4S)-4-(2-Methyl-3-oxohex-2-yl)-2,2-dimethyl-[1,3]dioxane

The solution of 207 mg (0.90 mmole) of a mixture of the compounds prepared according to Example 1l in 18 mL of anhydrous dichloromethane is treated with a molecular sieve (4A, approximately 20 spheres), 176 mg of N-methylmorpholino-N-oxide, 18 mg of tetrapropylammonium perruthenate and the mixture is stirred for 16 hours at 23°C under a dry argon atmosphere. The solution is evaporated and the obtained crude product is purified by chromatography on approximately 100 mL of fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 185 mg (0.81 mmole, 90%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.88 (3H), 1.04 (3H), 1.12 (3H), 1.22-1.37 (1H), 1.31 (3H), 1.40 (3H), 1.48-1.71 (3H), 2.46 (2H), 3.83 (1H), 3.96 (1H), 4.04 (1H) ppm.

Example 1n

4-tert.-Butyldimethylsilyloxy-but-2-yn-1-ol

To a solution of 100 g of 2-butyn-1-ol and 158 g of imidazole in 300 mL of dimethylformamide, a solution of 175 g of tert.-butyldimethylsilyl chloride in 100 mL of a 1:1 mixture of hexane and dimethylformamide is added dropwise slowly at 0°C under nitrogen and then the mixture is stirred for 2 hours at 0°C and for 16 hours at 22°C. The reaction mixture is diluted with 2.5 L of ether, washed once with water, once with 5% sulfuric acid, once with water, once with saturated sodium hydrogen carbonate solution and with half-saturated sodium chloride solution to neutrality. After drying over sodium sulfate and filtration, the solution is evaporated in vacuum. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-40% ether, 74.3 g of the compound in the title are obtained as a colorless oil.

IR (film): 3357, 2929, 2858, 1472, 1362, 1255, 1132, 1083, 1015, 837, 778 cm^{-1}

Example 1o

(4R,5S,2'S)-4-Methyl-5-phenyl-3-[1-oxo-2-methyl-6-(tert.-butyldimethylsilyloxy)-hex-4-yn-1-yl]-2-oxazolidinone

To 21 g of a solution of the silyl ether prepared according to Example 1n in 125 mL of toluene, 11.3 mL of lutidine are added under nitrogen. Then the mixture is cooled to -40°C and, at this temperature, 17.7 mL of trifluoromethanesulfonic acid anhydride are added dropwise. Then, the mixture is diluted with 100 mL of hexane and stirred for 10 minutes. This solution is added under nitrogen through a reversed sintered glass filter to a solution which was prepared from 17.8 g of hexamethyldisilazane in 140 mL of tetrahydrofuran with 73.5 mL of a 1.6 M solution of butyllithium in hexane at -60°C (10 minutes additional stirring time) and 23.3 g (4R,5S)-4-methyl-5-phenyl-3-propionyl-2-oxazolidinone in 62 mL of tetrahydrofuran (30 minutes of additional stirring). Stirring is continued for 1 hour at -60°C and then 6 mL of acetic acid in 5 mL of tetrahydrofuran are added and the reaction mixture is allowed to heat up to 22°C. It is poured into 80 mL of water and extracted three times with ether. The combined organic phases are washed twice with saturated sodium chloride solution and dried over sodium sulfate. After filtration, the mixture is evaporated in vacuum. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-20% ether, 16.0 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.10 (6H), 0.90 (9H), 0.92 (3H), 1.28 (3H), 2.47 (1H), 2.61 (1H), 3.96 (1H), 4.26 (2H), 4.78 (1H), 5.68 (1H), 7.31 (1H), 7.3-7.5 (3H) ppm.

Example 1p

(2S)-2-Methyl-6-(tert.-butyldimethylsilyloxy)-4-hexynoic acid ethyl ester

To a solution of 39.3 g of the alkylation product obtained according to Example 1o in 120 mL of ethanol, 9.0 mL of titanium(IV) ethylate are added under nitrogen and the mixture is heated under reflux for 4 hours. The reaction mixture is evaporated in vacuum and the residue is dissolved in 100 mL of ethyl acetate. Water, 3 mL, is added, the mixture is stirred for 20 minutes. The precipitate is filtered off under suction and is washed thoroughly with ethyl acetate. The filtrate is evaporated, 200 L of hexane are added and the precipitate is filtered off. The precipitate is washed thoroughly with hexane. The filtrate is evaporated in vacuum and the residue thus obtained is purified by chromatography on silica gel. With hexane/0-20% ether, 25.4 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR (CD_2Cl_2): δ: 0.10 (3H), 0.90 (9H), 1.2-1.3 (6H), 2.37 (1H), 2.54 (1H), 2.60 (1H), 4.12 (2H), 4.27 (2H) ppm.

Example 1q

(2S)-2-Methyl-6-(tert.-butyldimethylsilyloxy)-hexanoic acid ethyl ester

A solution of 10.5 g of the ester prepared according to Example 1p in 200 mL of ethyl acetate is treated with 1 g of 10% palladium on carbon and the mixture is stirred for 3 hours at 22°C in a hydrogen atmosphere. Then the catalyst is filtered off, washed thoroughly with ethyl acetate and the filtrate is evaporated in vacuum. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-10% ether, 9.95 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR (CD_2Cl_2): δ = 0.01 (6H), 0.84 (9H), 1.07 (3H), 1.18 (3H), 1.2-1.7 (6H), 2.38 (1H), 3.57 (2H), 4.05 (2H) ppm.

Example 1r

(2S)-2-Methyl-6-(tert.-butyldimethylsilyloxy)-hexan-1-ol

To a solution of 9.94 g of the ester prepared according to Example 1q in 130 mL of toluene, 63 mL of a 1.2 M solution of diisobutylaluminum hydride in toluene are added at -40°C under nitrogen and the mixture is stirred for 1 hour at this temperature. Then carefully 15

mL of isopropanol and after 10 minutes 30 mL of water are added, the temperature is allowed to come up to 22°C and stirring is continued at this temperature for 2 hours. The precipitate is filtered off, washed thoroughly with ethyl acetate and the filtrate is evaporated in vacuum. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-30% ether, 7.9 g of the compound in the title is obtained as a colorless oil.
$[\alpha]_D = -8.1°$ (c = 0.97, $CHCl_3$)
^{1}H-NMR ($CDCl_3$): δ = 0.07 (3H), 0.89 (9H), 0.91 (3H), 1.0-1.7 (7H), 3.48 (2H), 3.52 (2H) ppm.

Example 1s

(2S)-2-Methyl-6-(tert.-butyldimethylsilyloxy)-1-(tetrahydro-2H-pyran-2-yloxy)-hexane

To 6.4 g of the alcohol prepared according to Example 1r in 26 mL of methylene chloride, 3.52 mL of dihydropyrane, followed by 49 mg of p-toluenesulfonic acid monohydrate, are added at 0°C under argon. After stirring for 1.5 hours at 0°C, 10 mL of saturated sodium hydrogen carbonate solution are added and the mixture diluted with ether. The organic phase is washed twice with half-saturated sodium chloride solution and dried over sodium sulfate. After filtration, it is evaporated in vacuum and the residue thus obtained is purified by chromatography on silica gel. With hexane/0-5% ether, 4.75 g of the compound in the title are obtained as a colorless oil.
^{1}H-NMR ($CDCl_3$): δ = 0.05 (6H), 0.89 (9H), 0.92 (3H), 1.0-1.9 (13H), 3.19 (1H), 3.50 (1H), 3.55-3.65 (3H), 4.87 (1H), 4.57 (1H) ppm.

Example 1t

(5S)-5-Methyl-6-(tetrahydro-2H-pyran-2-yloxy)-hexan-1-ol

To a solution of 4.7 g of the THP ether in 170 mL tetrahydrofuran prepared according to Example 1s, 13.5 g of tetrabutylammonium fluoride trihydrate are added under nitrogen and stirring is continued for 3 hours. Then the reaction mixture is diluted with 800 mL of ether and washed three times using 20 mL of half-saturated sodium chloride solution each time and dried over sodium sulfate. After filtration, the mixture is evaporated in vacuum and the residue thus obtained is purified by chromatography on silica gel. With hexane/0-50% ethyl acetate, 2.88 g of the compound in the title are obtained as a colorless oil.
^{1}H-NMR (CD_2Cl_2): δ = 0.90/0.92 (3H), 1.1-1.9 (13H), 3.18 (1H), 3.40-3.65 (4H), 3.82 (1H), 4.53 (1H) ppm.

Example 1u

(5S)-5-Methyl-6-(tetrahydro-2H-pyran-2-yloxy)-hexanal

To 1.08 mL of oxalyl chloride, dissolved in 10 mL of methylene chloride, 1.9 mL of dimethylsulfoxide, dissolved in 7 mL of methylene chloride are added dropwise, carefully, under nitrogen at -70°C, followed by stirring for 10 minutes at this temperature. Then a solution of 2.0 g of the alcohol in 7 mL of methylene chloride prepared according to Example 1t are added dropwise and the mixture is stirred for 2 hours between -60°C and -70°C. Then, 3.86 mL of triethylamine are added and after 1 hour of stirring at -60°C, the reaction mixture is added to 30 mL of water. After phase separation, the aqueous phase is extracted twice using 30 mL of methylene chloride each time. The combined organic phases are washed three times with saturated sodium chloride solution. After drying over sodium sulfate and filtration, the mixture is evaporated in vacuum. Thus, 1.99 g of the aldehyde are obtained, which is used without further purification.

Example 1v

(2RS,6S)-6-Methyl-7-(tetrahydro-2H-pyran-2-yloxy)-heptan-2-ol

To a solution of 1.98 g of the aldehyde prepared according to Example 1u in 30 mL of ether, 6.16 mL of a 3 M methylmagnesium bromide solution in ether are added slowly under nitrogen at 0°C. After 60 minutes, the mixture is poured slowly into 50 mL of ice-cold saturated ammonium chloride solution and extracted three times with ether. The combined organic phases are washed once with water, twice with saturated sodium chloride solution and dried over sodium sulfate. After filtration, the mixture is evaporated in vacuum and the residue thus obtained is purified by chromatography on silica gel. With hexane/0-60% ether, 1.57 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR (CD_2Cl_2: δ = 0.90/0.93 (3H), 1.15 (3H), 1.0-1.9 (13H), 3.18 (1H), 3.4-3.6 (2H), 3.7-3.9 (2H), 4.53 (1H) ppm.

Example 1w

(2S,6RS)-2-Methyl-6-(tert.-butyldiphenylsilyloxy)-1-(tetrahydro-2H-pyran-2-yloxy)-heptane

To a solution of 1.57 g of the alcohol prepared according to Example 1v and 1.11 g of imidazole in 20 mL of dimethylformamide, 2.13 mL of tert.-butyldiphenylsilyl chloride are added at 0°C, under nitrogen, followed by stirring for 15 minutes at 0°C and for 16 hours at

22°C. The reaction mixture is diluted with 200 mL of ether, washed once with water, once with 10% sulfuric acid, once with saturated sodium hydrogen carbonate solution and with saturated sodium chloride solution to neutrality. After drying over sodium sulfate and filtration, the mixture is evaporated in vacuum. The residue thus obtained is purified by chromatography on silica gel. Using hexane/0-10% ether, 2.87 g of the compound in the title is obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.87/0.89 (3H), 1.04 (9H), 0.9-1.9 (16H), 3.15 (1H), 3.4-3.6 (2H), 3.8-3.9 (2H), 4.56 (1H), 7.3-7.5 (6H), 7.69 (4H) ppm.

Example 1x

(2S,6RS)-2-Methyl-6-(tert.-butyldiphenylsilyloxy)-heptan-1-ol

To a solution of 2.3 g of the silyl ether prepared according to Example 1w in 100 mL of ethanol, 131 mg of pyridinium-p-toluenesulfonate are added, followed by stirring for 4 hours at 40°C. Then the mixture is evaporated in vacuum and the residue thus obtained is purified by chromatography on silica gel. With hexane/20% ether, 1.68 g of the compound in the title are obtained as a colorless oil.

Example 1y

(2S,6RS)-2-Methyl-6-(tert.-butyldiphenylsilyloxy)-heptanal

The alcohol prepared under Example 1x, 2.13 g, is oxidized in analogy to Example 1u and, after work-up and chromatographic purification, 2.10 g of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.00-1.12 (15H), 1.18-1.63 (6H), 2.22 (1H), 3.83 (1H), 7.32-7.47 (6H), 7.61-7.72 (4H), 9.54 (1H) ppm.

Example 1z

(*S*)-Dihydro-3-hydroxy-2(3*H*)-furanone

10 g of L-(-)-malic acid are stirred in 45 mL of trifluoroacetic acid anhydride for 2 hours at 25°C. Then the mixture is evaporated in vacuum, 7 mL of methanol are added to the residue and stirring is continued for 12 hours. This is followed by evaporation in vacuum. The obtained residue is dissolved in 150 mL of absolute tetrahydrofuran. After cooling to 0°C, 150 mL of borane/tetrahydrofuran complex are added and stirring is continued for 2.5 hours at 0°C. Then 150 mL of methanol are added. Stirring is continued at room tempera-

ture for one hour and then the mixture is evaporated in vacuum. The obtained crude product is dissolved in 80 mL of toluene. Then 5 g of Dowex### (activated, acidic) are added and the mixture is boiled for 1 hour under reflux. Then the Dowex### is filtered off and the filtrate is evaporated in vacuum. The obtained crude product (7.61 g) is used in the next step without purification.

Example 1aa

(*S*)-Dihydro-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2(3*H*)-furanone

To a solution of 7.61 g of the substance described in Example 1z and 10 g of imidazole in 100 mL of *N,N*-dimethylformamide, 24 mL of *tert.*-butyldiphenylsilyl chloride are added. Stirring is continued for 2 hours at 25°C and the reaction mixture is poured into ice-cold saturated sodium hydrogen carbonate solution. After extraction with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After column chromatography of the crude product on silica gel with a mixture of hexane/ethyl acetate, 13.4 g of the compound in the title are obtained. ^{1}H-NMR ($CDCl_3$): δ = 7.72 (2H), 7.70 (2H), 7.40-7.50 (6H), 4.30-4.42 (2H), 4.01 (1H), 2.10-2.30 (2H), 1.11 (9H) ppm.

Example 1ab

(2RS,3*S*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]tetrahydro-2-furanol

To a solution of 13.4 g of the substance described in Example 1aa in 150 mL of absolute tetrahydrofuran, 80 mL of a 1 molar solution of diisobutylaluminum hydride in hexane are added at -78°C. Stirring is continued for 45 minutes at -78°C, followed by quenching with water. Then this is extracted with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. The compound in the title is obtained, 13.46 g, which is used in the next step without purification.

Example 1ac

(2RS,3*S*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1,4-pentanediol

To 20 mL of a 3 molar solution of methylmagnesium chloride in tetrahydrofuran, a solution of 13.46 g of the substance described in Example 1ab in 150 mL of absolute tetrahydrofuran is added dropwise at 0°C. Stirring is continued for one hour at 0°C and then the mixture is

poured into saturated aqueous ammonium chloride solution. This is extracted with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After column chromatography of the crude product of silica gel with a mixture of hexane/ethyl acetate, 11.42 g of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 7.65-7.75 (4H), 7.40-7.55 (6H), 5.20 (1H), 4.30 (2H), 3.70 (1H), 1.80 (2H), 1.05 (9H) ppm.

<u>Example 1ad</u>

(2RS,3*S*)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]-oxy]-2-pentanol

To a solution of 11.42 g of the substance described under Example 1ac and 3.25 g of 1*H*-imidazole in 120 mL of *N,N*-dimethylformamide, 4.9 g of *tert.*-butyldimethylsilyl chloride are added. The mixture is stirred for 2 hours at 25°C and then the reaction mixture is poured into ice-cold saturated sodium hydrogen carbonate solution. This is extracted with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After column chromatography of the crude product on silica gel with a mixture of hexane/ethyl acetate, 10.64 g of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 7.60-7.70 (4H), 7.30-7.45 (6H), 3.70-3.80 (2H), 3.40 (1H), 3.00 (1H), 1.80 (1H), 1.60 (1H), 1.05-1.12 (12H), 0.82 (9H), 0.02 (6H) ppm.

<u>Example 1ae</u>

(3*S*)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-pentanone

To 7.37 mL of oxalyl chloride in 80 mL of dichloromethane, 13 mL of dimethylsulfoxide are added at -78°C. Stirring is continued for 3 minutes and then 10.46 g of the substance described in Example 1ad in 100 mL of dichloromethane are added. After another 15 minutes of stirring time, 52 mL of triethylamine are added dropwise. Then the mixture is allowed to heat up to 0°C. Then the reaction mixture is poured into saturated sodium hydrogen carbonate solution. This is extracted with dichloromethane, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in

vacuum. After column chromatography of the crude product on silica gel with a mixture of hexane/ethyl acetate, 9.3 g of the compound in the title are obtained.
^{1}H-NMR ($CDCl_3$): δ = 7.60-7.70 (4H), 7.32-7.50 (6H), 4.25 (1H), 3.72 (1H), 3.58 (1H), 2.05 (3H), 1.90 (1H), 1.75 (1H), 1.13 (9H), 0.89 (9H), 0.01 (6H) ppm.

Example 1af

(E,3S)-1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene

The solution of 6.82 g of diethyl(2-methylthiazol-4-yl)methanephosphonate in 300 mL of anhydrous tetrahydrofuran is cooled under a dry argon atmosphere to -5°C and then 16.2 mL of a 1.6 molar solution of n-butyllithium in n-hexane is added, the mixture is allowed to warm up to 23°C and is stirred for 2 hours. Then it is cooled to -78°C, the solution of 6.44 g (13.68 mmole) of the compound prepared according to Example 1ae in 150 mL of tetrahydrofuran is added dropwise; the mixture is allowed to heat up to 23°C and is stirred for 16 hours. It is poured into saturated ammonium chloride solution, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 6.46 g (11.4 mmole, 83%) of the compound in the title are isolated as a colorless oil.
^{1}H-NMR ($CDCl_3$): δ = -0.04 (6H), 0.83 (9H), 1.10 (9H), 1.79 (1H), 1.90 (1H), 1.97 (3H), 2.51 (3H), 3.51 (2H), 4.38 (1H), 6.22 (1H), 6.74 (1H), 7.23-7.47 (6H), 7.63 (2H), 7.70 (2H) ppm.

Example 1ag

(E,3S)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-ol

The solution of 4.79 g (8.46 mmole) of the compound prepared according to Example 1af in 48 mL of tetrahydrofuran is treated with 48 mL of a 65:35:10 mixture of glacial acetic acid/water/tetrahydrofuran and is stirred for 2.5 days at 23°C. It is poured into saturated sodium carbonate solution, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography

on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 3.42 g (7.57 mole, 90%) of the compound in the title were isolated as a colorless oil.
^{1}H-NMR ($CDCl_3$): δ = 1.10 (9H), 1.53 (1H), 1.81 (2H), 1.96 (3H), 2.71 (3H), 3.59 (2H), 4.41 (1H), 6.38 (1H), 6.78 (1H), 7.26-7.49 (6H), 7.65 (2H), 7.72 (2H) ppm.

Example 1ah

(E,3S)-1-Iodine-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene

The solution of 8.41 g of triphenylphosphine in 120 mL of dichloromethane is treated at 23°C under a dry argon atmosphere with 2.19 g of imidazole, 8.14 g of iodine, the solution of 12.2 g (27.0 mmole) of the compound prepared according to Example 1ag in 30 mL of dichloromethane is added dropwise and the mixture is stirred for 0.5 hours. The solution is chromatographed on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 12.15 g (21.6 mmole, 80%) of the compound in the title are isolated as a colorless oil.
^{1}H-NMR ($CDCl_3$): δ = 1.08 (9H), 1.96 (3H), 2.10 (2H), 2.70 (3H), 2.87-3.08 (2H), 4.24 (1H), 6.32 (1H), 6.79 (1H), 7.28-7.48 (6H), 7.60-7.72 (4H) ppm.

Example 1ai

(5E,3S)-[3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-yl]-triphenylphosphonium iodide

The suspension of 12.55 g (22.3 mmole) of the compound prepared according to Example 1ah, 85 g of triphenylphosphine and 11.6 mL of N-ethyldiisopropylamine is stirred under a dry argon atmosphere for 16 hours at 80°C. After cooling, diethyl ether is added, the mixture is filtered and the residue is washed several times with diethyl ether and recrystallized from ethyl acetate. Thus, 15.7 g (19.1 mmole, 74%) of the compound in the title are isolated as a crystalline solid.
^{1}H-NMR ($CDCl_3$): δ = 1.07 (9H), 1.68-1.92 (2H), 1.98 (3H), 2.70 (3H), 2.93 (1H), 3.30 (1H), 4.53 (1H), 6.62 (1H), 7.03 (1H), 7.23-7.47 (6H), 7.48-7.72 (16H), 7.73-7.85 (3H) ppm.

Example 1ak

(4S(4R,5S,6S,10RS))-4-(2,6-Dimethyl-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-3-oxo-undec-2-yl)-2,2-dimethyl-[1,3]dioxane (A) and (4S(4S,5R,6S,10RS))-4-(2,6-dimethyl-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-3-oxo-undec-2-yl)-2,2-dimethyl-[1,3]dioxane (B)

The solution of 1.96 mL of diisopropylamine in 44 mL of anhydrous tetrahydrofuran is cooled in a dry argon atmosphere to -30°C, followed by the addition of 6.28 mL of a 2.4 molar solution of n-butyllithium in n-hexane and stirring for another 15 minutes. At -78°C, a solution of 3.08 g (13.47 mmole) of the compound prepared according to Example 1m in 44 mL of tetrahydrofuran are added dropwise and is allowed to react for 1 hour. Then, a solution of 5.77 g (15.1 mmole) of the compound prepared according to Example 1y in 44 mL of tetrahydrofuran is added and, after 45 minutes, the mixture is poured into saturated ammonium chloride solution. It is diluted with water, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After column chromatography on silica gel with a gradient system of n-hexane and ethyl acetate, in addition to 13% starting material, 4.03 g (5.92 mmole, 44%) of the compound in title A as well as 1.58 g (2.32 mmole, 17%) of a diastereoisomer B are obtained.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.79 (3H), 0.85 (3H), 0.90-1.10 (16H), 1.19-1.79 (10H), 1.26 (3H), 1.32 (3H), 1.38 (3H), 2.79 (1H), 3.18 (1H), 3.42 (1H), 3.78-3.92 (2H), 3.98 (1H), 4.17 (1H), 7.30-7.46 (6H), 7.62-7.72 (4H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.83 (3H), 0.91 (3H), 0.94-1.12 (16H), 1.19 (3H), 1.15-1.80 (10H), 1.31 (3H), 1.41 (3H), 2.54 (1H), 3.18 (1H), 3.47 (1H), 3.78-3.91 (2H), 3.97 (1H), 4.14 (1H), 7.31-7.47 (6H), 7.62-7.73 (4H) ppm.

Example 1al

(4S(4R,5S,6S,10RS))-4-(2,6-Dimethyl-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-3-oxo-5-(tetrahydropyran-2-yloxy)-undec-2-yl)-2,2-dimethyl-[1,3]dioxane

The solution of 4.02 g (6.58 mmole) of the compound prepared according to Example 1ak is reacted in analogy to Example 1a and, after work-up and purification, 4.26 g (6.13 mmole, 93%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.67-1.97 (47H), 3.02 + 3.12 (1H), 3.38 (1H), 3.48-4.04 (5H), 4.18 + 4.26 (1H), 4.42 + 4.50 (1H), 7.30-7.46 (6H), 7.61-7.72 (4H) ppm.

Example 1am

(4S(4R,5S,6S,10RS))-4-(2,6-Dimethyl-4-ethyl-10-hydroxy-3-oxo-5-(tetrahydropyran-2-yloxy)-undec-2-yl)-2,2-dimethyl-[1,3]dioxane

The solution of 4.26 g (6.13 mmole) of the compound prepared according to Example 1al is reacted in analogy to Example 1i and, after work-up and purification, 2.38 g (5.21 mmole, 85%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.78 + 0.84 (3H), 0.92-1.10 (6H), 1.13-1.98 (29H), 2.43 (1H), 3.06 + 3.18 (1H), 3.42 (1H), 3.60-4.04 (5H), 4.21 + 4.28 (1H), 4.42 + 4.54 (1H) ppm.

Example 1an

(4S(4R,5S,6S))-4-(3,10-Dioxo-2,6-dimethyl-4-ethyl-5-(tetrahydropyran-2-yloxy)-undec-2-yl)-2,2-dimethyl-[1,3]dioxane

The solution of 2.49 g (5.45 mmole) of the compound prepared according to Example 1am is reacted in analogy to Example 1m and, after work-up and purification, 2.24 g (4.93 mmole, 90%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.78 + 0.86 (3H), 0.90-1.37 (15H), 1.37-1.95 (15H), 2.13 (3H), 2.42 (2H), 3.07 + 3.18 (1H), 3.42 (1H), 3.60-4.04 (4H), 4.22 + 4.27 (1H), 4.41 + 4.53 (1H) ppm.

Example 1ao

(4S(4R,5S,6S,10E/Z,13S,14E))-4-(13-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-ethyl-15-(2-methyl-4-thiazolyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-2,6,10,14-tetramethylpentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane

The suspension of 4.92 g (5.97 mmole) of the compound prepared in analogy to Example 1ai, (5E,3S)-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-yl]-triphenylphosphonium iodide, in 14 mL of anhydrous tetrahydrofuran, is treated at 0°C in a dry argon atmosphere with 5.96 mL of a 1 M solution of sodium-bis-(trimethylsilyl)-amide in tetrahydrofuran and the mixture is allowed to heat up to 23°C. To the red solution, the solution of 877 mg (1.93 mmole) of the compound prepared according to Example 1an in 14 mL of tetrahydrofuran is added slowly, dropwise, followed by stirring for 2 hours, pouring into saturated ammonium chloride solution and extracting several times with ethyl acetate. The combined organic extracts are dried over sodium sulfate and evaporated in vacuum. After column chromatography on silica gel, with a gradient system

of n-hexane and ethyl acetate, in addition to 29% starting material, 732 mg (0.98 mmole, 51%) of the compound in the title are obtained.
^{1}H-NMR ($CDCl_3$): δ = 0.01 (3H), 0.05 (3H), 0.79 (3H), 0.81-1.02 (6H), 0.90 (9H), 1.04-1.38 (11H), 1.38-2.08 (19H), 1.60 (3H), 2.01 (3H), 2.16-2.34 (2H), 2.72 (3H), 3.06 + 3.17 (1H), 3.42 (1H), 3.68 (1H), 3.80-4.03 (3H), 4.03-4.32 (2H), 4.46 + 4.54 (1H), 5.13 (1H), 6.45 (1H), 6.92 (1H) ppm.

Example 1ap

(3S,6R,7S,8S,12E/Z,15S,16E)-6-Ethyl-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12,16-pentamethyl-heptadeca-12,16-diene-1,3,7,15-tetraol (A) and (3S,6R,7S,8S,12E/Z,15S,16E)-15-[[(1,1,-Dimethylethyl)dimethylsilyl]oxy]-6-ethyl-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12,16-pentamethyl-heptadeca-12,16-diene-1,3,7-triol(B)

The solution of 732 mg (0.98 mmole) of the compound prepared according to Example 1ao is reacted in analogy to Example 1f and, after work-up and purification, 98 mg (0.19 mmole, 20%) of compound A in the title as well as 380 mg (0.61 mmole, 62%) of compound B in the title are isolated as colorless oils.
^{1}H-NMR ($CDCl_3$) of A: δ = 0.79-0.95 (6H), 0.98-1.19 (4H), 1.21-1.86 (15H), 1.92-2.17 (5H), 2.33 (2H), 2.74 (3H), 2.87-3.23 (3H), 3.31-3.50 (1H), 3.65-3.92 (3H), 4.05-4.20 (2H), 5.10-5.25 (1H), 6.53 (1H), 6.96 (1H) ppm.
^{1}H-NMR ($CDCl_3$) of B: δ = 0.01 + 0.05 (6H), 0.80-0.96 (15H), 1.01-1.17 (4H), 1.20-1.68 (4H), 1.68-1.90 (10H), 1.90-2.16 (5H), 2.25 (2H), 2.73 + 2.77 (3H), 2.91 (1H), 3.19 (1H), 3.42 (1H), 3.61 (1H), 3.79-3.93 (3H), 3.99-4.19 (2H), 5.10 + 5.20 (1H), 6.42 (1H), 6.94 (1H) ppm.

Example 1aq

(3S,6R,7S,8S,12E/Z,15S,16E)-6-Ethyl-17-(2-methyl-4-thiazolyl)-4,4,8,12,16-pentamethyl-1,3,7,15-tetrakis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dien-5-one

The solution of 520 mg (approximately 0.86 mmole) of a mixture of the compounds A and B prepared according to Example 1ap in 25 mL of anhydrous dichloromethane is cooled in a dry argon atmosphere to -78°C, 2.6 mL of 2,6-lutidine and 2.57 mL of trifluoromethanesulfonic acid tert.-butyldimethylsilyl ester are added and the mixture is stirred for 16 hours. It is poured into saturated sodium hydrogen carbonate solution and extracted several times with

dichloromethane. The combined organic extracts are dried over sodium sulfate and evaporated in vacuum. After column chromatography on silica gel with a gradient system of n-hexane and ethyl acetate, 1.14 g (maximum 0.86 mmole, maximum 100%) of the title compound are isolated, which still contains silanol.

^{1}H-NMR ($CDCl_3$) of an analytically purified sample: ^{1}H-NMR ($CDCl_3$) δ = -0.04-0.11 (24H), 0.78-0.96 (42H), 1.13 (3H), 1.20 (3H), 1.02-1.65 (6H), 1.58 + 1.68 (3H), 1.72 (1H), 1.88-2.07 (2H), 2.00 (3H), 2.23 (2H), 2.71 (3H), 3.01 (1H), 3.52-3.73 (2H), 3.82 (1H), 3.91 (1H), 4.09 (1H), 5.13 (1H), 6.45 (1H), 6.91 (1H) ppm.

Example 1ar

(3S,6R,7S,8S,12E/Z,15S,16E)-3,7,15-6-Ethyl-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-1-hydroxy-17-(2-methyl-4-thiazolyl)-4,4,8,12,16-pentamethyl-heptadeca-12,16-dien-5-one

The solution of 1.14 g (maximum 0.86 mmole) of the compound, prepared according to Example 1aq in a mixture of 8 mL of dichloromethane and 8 mL of methanol, is treated at 0°C under a dry argon atmosphere with 204 mg of camphor-10-sulfonic acid, is allowed to warm up to 23°C and is stirred for another 1.5 hours. Then triethylamine is added, and the mixture is poured into a saturated sodium hydrogen carbonate solution and is extracted several times with dichloromethane. The combined organic extracts are dried over sodium sulfate and evaporated in vacuum. After column chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate, 618 mg (0.78 mmole, 90%) of the compound in the title are isolated.

^{1}H-NMR ($CDCl_3$): δ = -0.02-0.13 (18H), 0.77-0.98 (33H), 1.01-1.80 (10H), 1.08 (3H), 1.19 (3H), 1.55 + 1.66 (3H), 1.74-2.05 (2H), 2.00 (3H), 2.25 (2H), 2.70 (3H), 3.00 (1H), 3.68 (2H), 3.85 (1H), 4.08 (2H), 5.14 (1H), 6.44 (1H), 6.90 (1H) ppm.

Example 1as

(3S,6R,7S,8S,12E/Z,15S,16E)-6-Ethyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-methyl-4-thiazolyl)-5-oxo-heptadeca-12,16-dienal

The compound prepared according to Example 1ar, 510 mg (0.64 mmole), is reacted in analogy to Example 1k and, after work-up, 545 mg (maximum 0.64 mmole) of the compound in the title are isolated as crude product, which is reacted further without purification.

Example 1at

(3S,6R,7S,8S,12E/Z,15S,16E)-6-Ethyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-methyl-4-thiazolyl)-5-oxo-heptadeca-12,16-dienoicacid

The solution of 545 mg (maximum 0.64 mmole) of the compound prepared according to Example 1as in 15 mL of acetone is cooled to -30°C, treated with 460 μL of a standardized, 8 N chromium-sulfuric acid solution and is stirred for 1 hour. It is poured into a mixture of water and diethyl ether, the organic phase is washed with saturated sodium chloride solution and dried over sodium sulfate. After filtration and removal of the solvent, 410 mg (0.47 mmole, 74% based on the educt in Example 1as) of the compounds in the title, which can be separated by chromatography, are isolated as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) of the Z-isomer: δ = -0.02-0.15 (18H), 0.80-0.95 (33H), 1.03-2.28 (12H), 1.17 (3H), 1.18 (3H), 1.69 (3H), 1.96 (3H), 2.35 (1H), 2.54 (1H), 2.71 (3H), 3.03 (1H), 3.81 (1H), 4.16 (1H), 4.41 (1H), 5.20 (1H), 6.53 (1H), 6.94 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of the E-isomer: δ = -0.03-0.16 (18H), 0.79-0.95 (33H), 0.99-2.06 (10H), 1.17 (3H), 1.19 (3H), 1.57 (3H), 1.97 (3H), 2.26 (2H), 2.32 (1H), 2.61 (1H), 2.70 (3H), 3.09 (1H), 3.85 (1H), 4.09 (1H), 4.36 (1H), 5.12 (1H), 6.48 (1H), 6.94 (1H) ppm.

Example 1au

(3S,6R,7S,8S,12E/Z,15S,16E)-3,7-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-15-hydroxy-6-ethyl-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12,16-pentamethyl-heptadeca-12,16-dienoic acid

Variant I:

The solution of 310 mg (0.36 mmole) of the acid prepared according to Example 1at in 30 mL of anhydrous tetrahydrofuran is treated under a dry argon atmosphere with 500 μL of a hydrogen fluoride/pyridine complex, and 7.1 mL of a 1.1 M solution of tetrabutylammonium fluoride in tetrahydrofuran and stirred for 3 days at 50°C. It is poured into saturated ammonium chloride solution, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried over sodium sulfate. After filtration and removal of the solvent, the residue is purified by chromatography on approximately 200 mL of fine silica gel with a gradient system of dichloromethane and methanol. Thus, 125 mg (maximum 0.24 mmole, maximum 66%) are isolated, which still contain tetrabutylammonium salts.

Variant II:
In analogy to Example 1t, 32 mg (37 μmole) of the acid prepared in Example 1at is reacted and, after work-up and purification, 16 mg (31 μmole, 83%) of the compound in the title are isolated as a colorless oil.
^{1}H-NMR ($CDCl_3$) of the Z isomer: δ = 0.01-0.14 (12H), 0.80-0.99 (24H), 1.02-1.67 (7H), 1.18 (3H), 1.19 (3H), 1.70 (1H), 1.73 (3H), 1.97 (1H), 2.01 (3H), 2.14 (1H), 2.27-2.40 (3H), 2.53 (1H), 2.71 (3H), 2.81 (1H), 3.01 (1H), 3.82 (1H), 4.17 (1H), 4.48 (1H), 5.19 (1H), 6.69 (1H), 6.95 (1H) ppm.
^{1}H-NMR ($CDCl_3$) of the E isomer: δ = -0.02-0.11 (12H), 0.73-0.95 (24H), 1.00-1.63 (7H), 1.12 (3H), 1.17 (3H), 1.60 (3H), 1.71 (1H), 1.89-2.06 (2H), 2.00 (3H), 2.22-2.39 (3H), 2.53 (1H), 2.69 (3H), 2.79 (1H), 3.02 (1H), 3.79 (1H), 4.15 (1H), 4.34 (1H), 5.15 (1H), 6.56 (1H), 6.92 (1H) ppm.

Example 1aw

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dione

The solution of 55 mg (73 μmole) of the compound prepared according to Example 1au in 0.8 mL of anhydrous tetrahydrofuran is treated in a dry argon atmosphere with 46 μL of triethylamine, 44 μL of 2,4,6-trichlorobenzoyl chloride and stirred for 20 minutes. Then, this is diluted with 20 mL of tetrahydrofuran, 68 mg of 4-dimethylaminopyridine are added and the mixture is stirred for 30 minutes at 23°C. It is evaporated to dryness, taken up in a little dichloromethane and purified by chromatography on 100 mL of fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 49 mg (65 μmole, 89%) of the compounds in the title are isolated as colorless oil.
^{1}H-NMR ($CDCl_3$) of the Z-isomer: δ = -0.12 (3H), 0.08 (3H), 0.10 (3H), 0.13 (3H), 0.73 (3H), 0.79-1.78 (7H), 0.85 (9H), 0.93 (9H), 0.99 (3H), 1.10 (3H), 1.18 (3H), 1.67 (3H), 1.88 (1H), 2.05 (1H), 2.09 (3H), 2.45 (1H), 2.54-2.74 (2H), 2.69 (3H), 2.77 (1H), 3.08 (1H), 4.00 (2H), 4.56 (1H), 5.16 (1H), 6.56 (1H), 6.95 (1H) ppm.
^{1}H-NMR ($CDCl_3$) of the E isomer: δ = 0.02-0.16 (12H), 0.78-1.00 (24H), 1.09 (3H), 1.14-1.93 (8H), 1.20 (3H), 1.59 (3H), 2.09-2.21 (1H), 2.13 (3H), 2.39 (1H), 2.43-2.64 (3H), 2.70 (3H), 2.98 (1H), 3.95 (1H), 4.40 (1H), 5.21 (1H), 5.29 (1H), 6.51 (1H), 6.92 (1H) ppm.

Example 1

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dione (A) and (4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dione (B)

The solution of 48 mg (64 μmole) of the compound prepared according to Example law in 3 mL of anhydrous dichloromethane is treated at -20°C under a dry argon atmosphere with 220 μL of approximately 20% trifluoroacetic acid, followed by stirring for 1 hour. It is poured into a saturated sodium hydrogen carbonate solution, extracted with dichloromethane and the organic phase is dried over sodium sulfate. After filtration and removal of the solvent, the residue is purified by repeated chromatography on analytical thin-layer plates. A mixture of n-hexane and ethyl acetate is used as solvent, and ethyl acetate as eluting agent. Thus, 13 mg (25 μmole, 39%) of compound A in the title as well as 12 mg (23 μmole, 36%) of compound B in the title are isolated, each as a colorless oil.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.89 (3H), 1.04 (3H), 1.09 (3H), 1.19-1.94 (8H), 1.33 (3H), 1.70 (3H), 2.07 (3H), 2.15-2.33 (2H), 2.38 (1H), 2.44-2.74 (3H), 2.70 (3H), 3.23 (1H), 3.62 (1H), 3.72 (1H), 4.24 (1H), 5.12 (1H), 5.22 (1H), 6.57 (1H), 6.95 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.84 (3H), 1.01 (6H), 1.29 (3H), 1.38-2.00 (8H), 1.61 (3H), 2.07 (3H), 2.20 (1H), 2.22-2.50 (3H), 2.58 (1H), 2.70 (3H), 3.37 (1H), 3.73 (1H), 4.02 (1H), 4.12 (1H), 4.41 (1H), 5.05 (1H), 5.38 (1H), 6.57 (1H), 6.99 (1H) ppm.

Example 2

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and (1R,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B)

The solution of 10 mg (19 μmole) of compound A prepared according to Example 1 in 1 mL of dichloromethane is treated in a dry argon atmosphere at -10°C with 10 mg of an approximately 80% meta-chloroperbenzoic acid and is stirred for 4 hours at 0°C. It is poured into a saturated sodium hydrogen carbonate solution, extracted with dichloromethane and the organic phase is dried over sodium sulfate. After filtration and removal of the solvent, the

residue is purified by repeated chromatography on analytical thin-layer plates. Mixtures of n-hexane and ethyl acetate as well as dichloromethane and methanol serve as solvents, and ethyl acetate as eluting agent. Thus, 4.5 mg (8.4 μmole, 44%) of compound A in the title as well as 1 mg (1.9 μmole, 10%) of compound B in the title are isolated as a colorless foam.
^{1}H-NMR ($CDCl_3$) of A: δ = 0.86 (3H), 1.00 (3H), 1.05 (3H), 1.28 (3H), 1.33-2.12 (10H), 1.38 (3H), 2.11 (3H), 2.41 (1H), 2.57 (1H), 2.70 (3H), 2.77-2.85 (2H), 3.38 (1H), 3.49 (1H), 3.49 (1H), 3.67 (1H), 4.27 (1H), 4.56 (1H), 5.46 (1H), 6.57 (1H), 6.97 (1H) ppm.
^{1}H-NMR ($CDCl_3$) of B: δ = 0.85 (3H), 0.95 (3H), 1.03 (3H), 1.22-1.73 (10H), 1.30 (3H), 1.38 (3H), 2.08 (1H), 2.61 (3H), 2.41-2.59 (2H), 2.71 (3H), 2.91 (1H), 2.99 (1H), 3.24 (1H), 3.24 (1H), 3.43 (1H), 3.96 (1H), 4.30 (1H), 5.60 (1H), 6.60 (1H), 6.98 (1H) ppm.

Example 3

(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and (1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B)

Compound B, prepared according to Example 1, 10 mg (19 μmole), is reacted in analogy to Example 2 and, after work-up and purification, 6 mg (11 μmole, 59%) of a mixture of the two compounds in the title are isolated as a colorless foam.
^{1}H-NMR ($CDCl_3$) of A or B: δ = 0.86 (3H), 0.96 (3H), 1.03 (3H), 1.06-2.08 (11H), 1.28 (3H), 1.38 (3H), 2.09 (3H), 2.46-2.59 (2H), 2.70 (3H), 2.87 (1H), 3.02 (1H), 3.33 (1H), 3.79 (1H), 4.22 (1H), 4.34 (1H), 5.49 (1H), 6.65 (1H), 7.00 (1H) ppm.
^{1}H-NMR ($CDCl_3$) of B or A: δ = 0.86 (3H), 0.96 (3H), 1.09 (3H), 1.21-1.94 (9H), 1.25 (3H), 1.37 (3H), 2.03 (2H), 2.09 (3H), 2.50-2.61 (2H), 2.71 (3H), 2.87 (1H), 2.94 (1H), 3.28 (1H), 3.67 (1H), 3.72 (1H), 4.27 (1H), 5.46 (1H), 6.59 (1H), 6.97 (1H) ppm.

Example 4

(4S,7S,8R,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione (A) and (4S,7S,8R,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione (B)

The diastereoisomeric compound B prepared according to Example 1ak is reacted in analogy to Examples 1al to 1aw and 1 to obtain the compounds A and B in the title.

Example 5

(1S,3S(E),7S,10S,11R,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and
(1R,3S(E),7S,10S,11R,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B)

The compound A prepared according to Example 4 is reacted in analogy to Example 2 to form the separable title compounds A and B.

Example 6

(1S,3S(E),7S,10S,11R,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and
(1R,3S(E),7S,10S,11R,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

The compound B prepared according to Example 4 is reacted in analogy to Example 2 to form a mixture of the compounds in the title.

Example 7

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione (A) and
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione (B)

Example 7a

(Z,3S)-1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(3-pyridyl)-pent-4-ene (A) and
(E,3S)-1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(3-pyridyl)-pent-4-ene (B)

In analogy to Example 1af, 4.8 g (10.2 mmole) of the compound prepared according to Example 1ae is reacted using diethyl(3-pyridyl)methanephosphonate and, after work-up and purification, 448 mg (0.82 mmole, 8%) of compound A in the title, as well as 3.5 g (6.41 mmole, 63%) of compound B in the title are isolated, each as a colorless oil.

^{1}H-NMR ($CDCl_3$) of A: δ = -0.06 (6H), 0.81 (9H), 1.01 (9H), 1.75 (1H), 1.97 (4H), 3.48 (2H), 4.83 (1H), 6.11 (1H), 6.97 (1H), 7.11-7.30 (5H), 7.30-7.39 (2H), 7.39-7.50 (4H), 8.08 (1H), 8.33 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = -0.01 (6H), 0.85 (9H), 1.11 (9H), 1.78 (3H), 1.83 (1H), 1.97 (1H), 3.58 (2H), 4.42 (1H), 6.03 (1H), 7.21 (1H), 7.28-7.50 (7H), 7.62-7.75 (4H), 8.29 (1H), 8.41 (1H) ppm.

Example 7b

(E,3S)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(3-pyridyl)-pent-4-en-1-ol

Analogously to Example 1ag, 3.5 g (6.41 mmole) of the compound prepared according to Example 7aB in the German; should it be 7ab?], reacted with a 65:35:10 mixture of glacial acetic acid/water/tetrahydrofuran. Thus, after purification, 2.1 g (4.86 mmole, 76%) are obtained.

^{1}H-NMR ($CDCl_3$): δ = 1.12 (9H), 1.75 (3H), 1.88 (2H), 3.65 (2H), 4.45 (1H), 6.25 (1H), 7.21 (1H), 7.28-7.50 (7H), 7.60-7.75 (4H), 8.30 (1H), 8.44 (1H) ppm.

Example 7c

(E,3S)-1-Iodine-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(3-pyridyl)-pent-4-ene

Analogously to Example 1ah, starting from 2.1 g (4.86 mmole) of the compound described under Example 7b, 1.98 g (3.66 mmole, 75%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 1.11 (9H), 1.78 (3H), 2.17 (2H), 3.03 (2H), 4.29 (1H), 6.19 (1H), 7.22 (1H), 7.30-7.50 (7H), 7.63-7.75 (4H), 8.32 (1H), 8.44 (1H) ppm.

Example 7d

(5E,3S)-[3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(3-pyridyl)-pent-4-en-1-yl]-triphenylphosphonium iodide

Analogously to Example 1ai, starting from 1.98 g (3.66 mmole) of the compound described in Example 7c, 2.35 g (2.93 mmole, 80%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$: δ = 1.08 (9H), 1.80 (3H), 3.27 (1H), 3.56 (1H), 4.66 (1H), 6.52 (1H), 7.25-7.90 (27H), 8.35 (1H), 8.46 (1H) ppm.

Example 7e

(4S(4R,5S,6S,10E/Z,13S,14E))-4-(13-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]2,4,6,10,14-pentamethyl-15-(3-pyridyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane

Analogously to Example 1ao, 800 mg (1.76 mmole) the compound prepared in analogy to the examples 1l (reaction with ethyl magnesium bromide) to 1an, (4S(4R,5S,6S))-4-(3,10-dioxo-2,4,6-trimethyl-5-(tetrahydropyran-1-yloxy)-undec-2-yl)-2,2-dimethyl-[1,3]dioxane with is reacted 4.24 g (5.28 mmole) of the compound described in Example 7d and 5.44 mL of a 1 M solution of sodium-bis-(trimethylsilyl)-amide in tetrahydrofuran. Thus, 684 mg (0.79 mmole, 45%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.86-0.98 (3H), 0.98-1.94 (45H), 2.20-2.42 (2H), 3.22 (1H), 3.42 (1H), 3.58-4.02 (4H), 4.08-4.22 (2H), 4.46 + 4.52 (1H), 5.00 (1H), 6.03 (1H), 7.19 (1H), 7.24-7.47 (7H), 7.60-7.73 (4H), 8.28 + 8.40 (2H) ppm.

Example 7f

(3S,6R,7S,8S,12E/Z,15S,16E)-15-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4,4,6,8,12,16-hexamethyl-17-(3-pyridyl)-5-oxo-heptadeca-12,16-diene-1,3,7-triol

Analogously to Example 1ap, starting from 684 mg (0.79 mmole) of the compound described in Example 7e, 542 mg (0.73 mmole, 92%) of the compound in the title are obtained.

Example 7g

(3S,6R,7S,8S,12E/Z,15S,16E)-15-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4,4,6,8,12,16-hexamethyl-17-(3-pyridyl)-1,3,7-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dien-5-one

Analogously to Example 1aq, starting from 542 mg (0.73 mmole) of the compound described in Example 7f, 995 mg (maximum 0.73 mole, maximum 100%) of the compound in the title are obtained, which is contaminated with silanol.

Example 7h

(3S,6R,7S,8S,12E/Z,15S,16E)-3,7-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-15-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-hydroxy-4,4,6,8,12,16-hexamethyl-17-(3-pyridyl)-heptadeca-12,16-dien-5-one

Analogously to Example 1ar, starting from 995 mg (maximum 0.73 mmole) of the compound described in Example 7g, 604 mg (0.62 mmole, 85%) of the compound in the title are obtained.

Example 7i

(3S,6R,7S,8S,12E/Z,15S,16E)-3,7-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-15-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4,4,6,8,12,16-hexamethyl-17-(3-pyridyl)-5-oxo-heptadeca-12,16-dienoic acid

Analogously to Examples 1as and 1at, starting from 604 mg (0.62 mmole) of the compound described in Example 7h, 550 mg (0.56 mmole, 90%) of the compound in the title are obtained.

Example 7k

(3S,6R,7S,8S,12E/Z,15S,16E)-4,4,6,8,12,16-Hexamethyl-17-(3-pyridyl)-5-oxo-3,7,15-trihydroxy-heptadeca-12,16-dienoic acid

Analogously to Example 1au, starting from 550 mg (0.56 mmole) of the compound described under Example 7i, 269 mg (0.49 mmole, 88%) of the compound in the title are obtained.

Example 7l

(3S,6R,8S,12E/Z,15S,16E)-3,7-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-15-hydroxy-17-(3-pyridyl)-5-oxy-heptadeca-12,16-dienoic acid

Analogously to Example 1av, starting from 269 mg (0.49 mmole) of the compound described in Example 7k, 127 mg (0.17 mmole, 35%) of the compound in the title are obtained.

Alternative preparation of 7l by 7n to 7r:

Example 7n

(4S(4R,5S,6S,10E/Z,13S,14E))-4-(13-hydroxy-2,4,6,10,14-pentamethyl-15-(3-pyridinyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane

Analogously to Example 1i, starting from 710 mg (0.85 mmole) of the compound described under 7e, 486 mg (0.81 mmole, 95%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.90-1.00 (3H), 1.05-1.90 (36H), 2.38 (2H), 3.27 (1H), 3.46 (1H), 3.63 + 3.80-4.00 (4H), 4.10-4.20 (2H), 4.46 + 4.55 (1H), 5.15 (1H), 6.49 (1H), 7.24 (1H), 7.57 (1H), 8.47 (1H), 8.54 (1H) ppm.

Example 7o

(3S,6R,7S,8S,12E/Z,15S,16E)-4,4,6,8,12,16-hexamethyl-17-(3-pyridyl)-1,3,7,15-tetra-hydroxy-heptadeca-12,16-dien-5-one

Analogously to Example 1f, starting from 486 mg (0.81 mmole) of the compound described in 7n, 335 mg (0.71 mmole, 87%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.82 + 0.86 (3H), 1.08 + 1.10 (3H), 1.13 (3H), 1.22 (3H), 1.68 + 1.72 (3H), 1.90 (3H), 2.40 (2H), 3.30 (1H), 3.35-3.48 (2H), 3.85-3.96 (2H), 4.17 (1H), 4.20 (1H), 5.05 (1H), 6.50 (1H), 7.25 (1H), 7.61 (1H), 8.45 (1H), 8.53 (1H) ppm.

Example 7p

(3S,6R,7S,8S,12E/Z,15S,16E)-3,7,15-Tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-1-hydroxy-4,4,6,8,12,16-hexamethyl-17-(3-pyridyl)-heptadeca-12,16-dien-5-one

Analogously to Example 1aq, starting from 335 mg (0.71 mmole) of the compound described under 7o, 730 mg (maximum 0.71 mmole, maximum 100%) of the compound in the title are obtained, which is contaminated with silanol.

^{1}H-NMR ($CDCl_3$): δ = 0.05-1.16 (24H), 0.85-0.97 (39H), 1.02 + 1.04 + 1.07 (6H), 1.22 (3H), 1.60 (3H), 1.70 + 1.83 (3H), 2.29 (1H), 3.13 (1H), 3.05-3.80 (2H), 3.76 (1H), 3.89 (1H), 4.11 (1H), 5.13 (1H), 6.46 (1H), 7.23 (1H), 7.54 (1H), 8.42 (1H), 8.50 (1H9 [as in German text, believe it should be (1H) - T.] ppm.

Example 7q

(3S,6R,7S,8S,12E/Z,15S,16E)-3,7,15-Tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-1-hydroxy-4,4,6,8,12,16-hexamethyl-17-(3-pyridyl)-heptadeca-12,16-dien-5-one

Analogously to Example 1ar, starting from 730 mg (maximum 0.71 mmole) of the compound described under 7p, 441 mg (0.54 mmole, 76%) of the compound in the title are obtained.
^{1}H-NMR ($CDCl_3$): δ = 0.05-0.18 (18H), 0.90-1.10 (30H), 1.11 (6H), 1.25 (3H), 1.62 + 1.70 (3H), 1.82 (3H), 2.38 (1H), 3.13 (1H), 3.63 (2H), 3.81 (1H), 4.05-4.15 (2H), 5.17 (1H), 6.38 (1H), 7.22 (1H), 7.53 (1H), 8.45 (1H), 8.52 (1H) ppm.

Example 7r

(3S,6R,7S,8S,12E/Z,15S,16E)-3,7,15-Tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-17-(3-pyridyl)-5-oxo-heptadeca-12,16-dienoic acid

Analogously to the Examples 1as and 1at, starting from 441 mg (0.38 mmole) of the compound described under 7q, 316 mg (0.38 mmole, 70%) of the compound in the title are obtained.
^{1}H-NMR ($CDCl_3$): δ = 0.00-0.18 (18H), 0.90-1.00 (30H), 1.12 (3H), 1.13 + 1.14 (3H), 1.19 (3H), 1.62 + 1.70 (3H), 1.79 + 1.80 (3H), 3.18 (1H), 3.75 + 3.80 (1H), 4.19 (1H), 4.44 + 4.48 (1H), 5.12 + 5.14 (1H), 6.32 + 6.35 (1H), 7.30 (1H), 7.60 + 7.62 (1H), 8.38 + 8.40 (1H), 8.58 ppm.

Example 7l

(3S,6R,8S,12E/Z,15S,16E)-3,7-Bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-15-hydroxy-17-(3-pyridyl)-5-oxy-heptadeca-12,16-dienoic acid

Analogously to Example 1i, starting from 316 mg (0.38 mmole) of the compound described under 7r, 295 mg (maximum 0.38 mmole, maximum 100%) of the compound in the title are obtained.
^{1}H-NMR ($CDCl_3$): δ = 0.00-0.18 (12H), 0.88-1.00 (21H), 1.10 (3H), 1.15 (3H), 1.18 (3H), 1.63 + 1.70 (3H), 1.84 + 1.86 (3H), 2.30-2.50 (3H), 3.10 (1H), 3.75 + 3.78 (1H), 4.20 + 4.25 (1H), 4.45 (1H), 5.14 (1H), 6.49 (1H), 7.33 (1H), 7.68 (1H), 8.41 (1H), 8.60 (1H) ppm.

Example 7m

(4S,7R,8S,13E/Z,16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-16-((3-pyridyl)ethenyl)1-oxa-cyclohexadec-13-ene-2,6-dione

Analogously to Example 1aw, starting from 127 mg (0.17 mmole) of the compound described under Example 7l, 104 mg (0.14 mmole, 85%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = -0.05-0.13 (12H), 0.82-1.00 (21H), 1.12 (3H), 1.15 (3H), 1.23 (3H), 1.60 + 1.69 (3H), 1.90 + 1.92 (3H), 2.40-2.60 (4H), 3.02 (1H), 3.88 + 3.90 (1H), 4.10 (1H), 4.48 (1H), 5.07 + 5.14 (1H), 5.18 + 5.25 (1H), 6.47 + 6.50 (1H), 7.25 (1H), 7.55 + 7.60 (1H), 8.45 (1H), 8.50 + 8.53 (1H) ppm.

Example 7

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione (A) and (4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione (B)

Analogously to Example 1, starting from 104 mg (0.14 mmole) of the compound described in Example 7m, 24 mg (48 μmole, 34%) of compound A in the title as well as 25 mg (50 μmole, 36%) of compound B in the title are obtained.

^{1}H-NMR ($CDCl_3$)

Compound A: δ = 1.03 (3H), 1.10 (3H), 1.21 (3H), 1.32 (3H), 1.62 (3H), 1.92 (3H), 2.18-2.80 (6H), 3.14 (1H), 3.73 (1H), 4.16 (1H), 5.17 (1H), 5.29 (1H), 6.51 (1H), 7.25 (1H), 7.58 (1H), 8.47 (1H), 8.53 (1H) ppm.

Compound A [sic, B?]: δ = 1.00 (3H), 1.05 (3H), 1.16 (3H), 1.30 (3H), 1.63 (3H), 1.91 (3H), 2.18-2.65 (6H), 3.22 (1H), 3.65 (1H), 4.20 (1H), 5.11 (1H), 5.43 (1H), 6.49 (1H), 7.27 (1H), 7.59 (1H), 8.49 (1H), 8.52 (1H) ppm.

Example 8

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((3-pyridyl)-ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and
(1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((3-pyridyl)-ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B) and
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((3-N-oxypyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (C) and
(1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((3-N-oxypyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (D)

Analogously to Example 2, starting from 15 mg (30 μmole) of compound A described in Example 7, 7.4 mg (14 μmole, 46%) of compound A in the title, 1.6 mg (3 μmole, 10%) of compound B in the title, 2.4 mg of compound C in the title, as well as 0.9 mg (4.4 mmole, 15%) of compound D in the title (1.7 mg, 6%) are obtained.

^{1}H-NMR ($CDCl_3$): Compound C:
δ = 1.03 (3H), 1.10 (3H), 1.17 (3H), 1.28 (3H), 1.22 (3H), 1.91 (3H), 2.40-2.63 (3H), 2.79 (1H), 3.33 (1H), 3.68 (1H), 3.77 (1H), 4.12 (3H), 5.46 (1H), 6.46 (1H), 7.18 (1H), 7.25 (1H), 8.11 (1H), 8.18 (1H) ppm.

Compound D:
δ = 0.97 (3H), 1.10 (3H), 1.13 (3H), 1.28 (3H), 1.40 (3H), 1.95 (3H), 2.50 (1H), 3.12 (1H), 3.34 (1H), 3.80 (1H), 4.08 (1H), 4.16 (1H), 5.69 (1H), 6.47 (1H), 7.17 (1H), 7.26 (1H), 8.11 (1H), 8.18 (1H) ppm.

Example 9

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione (A) and
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione (B)

Example 9a

(4S(4R,5S,6S,10E/Z,13S,14E))-4-(13-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]2,4,6,10,14-pentamethyl-15-(4-pyridyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane

Analogously to Example 7e, 2.08 g (4.70 mmole) of the compound prepared in Examples 1l (reaction with ethylmagnesium bromide) to 1an, (4S(4R,5S,6S))-4-(3,10-dioxo-2,4,6-trimethyl-5-(tetrahydropyran-2-yloxy)-undec-2-yl-2,2-dimethyl-[1,3]dioxane, are reacted with 11.4 g (14.2 mmole) of (5E,3S)-[3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(4-pyridyl)-pent-4-en-1-yl]-triphenylphosphonium iodide, which was prepared in analogy to Examples 7a to 7d using diethyl(4-pyridyl)methanephosphonate. After work-up and purification, 2.10 g (2.5 mmole, 53%) of the compound in the title are isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.81-1.95 (49H), 2.20-2.42 (2H), 3.23 (1H), 3.42 (1H), 3.58-4.02 (3H), 4.06-4.21 (2H), 4.46 + 4.52 (1H), 4.99 (1H), 6.03 (1H), 6.94 (2H), 7.22-7.48 (6H), 7.59-7.73 (4H), 8.49 (2H) ppm.

Example 9b

(4S(4R,5S,6S,10E/Z,13S,14E))-4-(13-Hydroxy-2,4,6,10,14-pentamethyl-15-(4-pyridyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-pentadeca-10,14-dien-2-yl)-2,2-dimethyl[1,3]dioxane

Analogously to Example 1i, starting from 780 mg (0.93 mmole) of the compound described in Example 9a, 550 mg (0.91 mmole, 98%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$: δ = 0.80-1.85 (33H), 1.91 (3H), 1.94-2.11 (5H), 2.36 (2H), 3.27 (1H), 3.43 (1H), 3.61-4.01 (3H), 4.08-4.21 (2H), 4.46 + 4.54 (1H), 5.16 (1H), 6.48 (1H), 7.18 (2H), 8.55 (2H) ppm.

Example 9c

(3S,6R,7S,8S,12E/Z,15S,16E)-4,4,6,8,12,16-Hexamethyl-17-(4-pyridyl)-1,3,7,15-tetra-hydroxy-heptadeca-12,16-dien-5-one

Analogously to Example 1f, starting from 600 mg (1.00 mmole) of the compound described in Example 9b using p-toluenesulfonic acid, 340 mg (0.71 mmole, 71%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.82 (3H), 1.06 (3H), 1.12 (3H), 1.22 (3H), 1.73 (3H), 0.90-1.83 (9H), 1.91 (3H), 1.95-2.13 (3H), 2.30-2.47 (2H), 3.19-3.35 (2H), 3.42 (1H), 3.81-3.97 (2H), 4.04 (1H), 4.19 (1H), 5.18 (1H), 6.46 (1H), 7.18 (2H), 8.52 (2H) ppm.

Example 9d

(3S,6R,7S,8S,12E/Z,15S,16E)-3,7,15-Tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-1-hydroxy-4,4,6,8,12,16-hexamethyl-17-(4-pyridyl)-heptadeca-12,16-dien-5-one

Analogously to Example 1aq, starting from 300 mg (0.63 mmole) of the compound described in Example 9c, 435 mg (0.47 mmole, 74%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = -0.01-0.14 (24H), 0.82-0.97 (37H), 1.02 (3H), 1.04 (3H), 1.21 (3H), 0.98-1.70 (12H), 1.87 (3H), 1.90-2.03 (2H), 2.25 (2H), 3.13 (1H), 3.51-3.71 (2H), 3.76 (1H), 3.88 (1H), 4.03-4.14 (1H), 5.13 (1H), 6.34 (1H), 7.13 (2H), 8.52 (2H) ppm.

Example 9e

(3S,6R,7S,8S,12E/Z,15S,16E)-3,7,15-Tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-1-hydroxy-4,4,6,8,12,16-hexamethyl-17-(4-pyridyl)-heptadeca-12,16-dien-5-one

Analogously to Example 1ar, starting from 410 mg (0.44 mmole) of the compound described in Example 9d, 339 mg (0.41 mmole, 94%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = -0.01-0.14 (18H), 0.80-0.95 (31H), 0.97-1.70 (7H), 1.06 (6H), 1.21 (3H), 1.59 + 1.69 (3H), 1.87 (3H), 1.90-2.06 (2H), 2.26 (2H), 3.12 (1H), 3.65 (2H), 3.80 (1H), 4.09 (2H), 5.14 (1H), 6.36 (1H), 7.13 (2H), 8.53 (2H) ppm.

Example 9f

(3S,6R,7S,8S,12E/Z,15S,16E)-3,7,15-Tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-17-(4-pyridyl)-5-oxo-heptadeca-12,16-dienoic acid

Analogously to the Examples 1as and 1at, starting from 280 mg (0.34 mmole) of the compound described under 9e, 204 mg (0.25 mmole, 72%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.00-0.14 (18H), 0.78-0.98 (30H), 1.06 (3H), 1.08 (3H), 1.24 (3H), 1.05-1.55 (5H), 1.60 + 1.69 (3H), 1.87 (3H), 1.98 (2H), 2.20-2.37 (3H), 2.10-3.10 (1H), 2.51 (1H), 3.14 (1H), 3.79 (1H), 4.11 (1H), 4.40 (1H), 5.13 (1H), 6.36 (1H), 7.17 (2H), 8.53 (2H) ppm.

Example 9g

(3S,6R,8S,12E/Z,15S,16E)-3,7-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-15-hydroxy-17-(4-pyridyl)-5-oxy-heptadeca-12,16-dienoic acid

Analogously to Example 1av, starting from 198 mg (0.24 mmole) of the compound described in Example 9f, 132 mg (0.18 mmole, 77%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.00-0.15 (12H), 0.85-1.00 (18H), 1.10-1.18 (6H), 1.20-1.28 (6H), 1.62 + 1.73 (3H), 2.05 (1H), 2.20-2.50 (4H), 2.85 (1H), 3.15 (1H), 3.79 (1H), 4.18 (1H), 4.42 (1H), 5.18 (1H), 6.50 (1H), 7.15-7.25 (2H), 8.50-8.60 (2H) ppm.

Example 9h

(4S,7R,8S,13E/Z,16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-16-((4-pyridyl)ethenyl)-1-oxacyclohexadec-13-ene-2,6-dione

Analogously to Example 1aw, starting from 130 mg (0.18 mmole) of the compound described in Example 9g, 98 mg (0.14 mmole, 76%) of the compound in the title are obtained.

Example 9

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxacyclohexadec-13-ene-2,6-dione (A) and (4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxacyclohexadec-13-ene-2,6-dione (B)

Analogously to Example 1, starting from 98 mg (0.14 mmole) of the compound described in Example 9h, 24 mg (49 μmole, 35%) of compound A in the title as well as 21 mg (43 μmole, 31%) of compound B in the title are obtained.

Example 10

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12-16-pentamethyl-3-((4-pyridyl)-ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and (1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((4-pyridyl)-ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B)

Analogously to Example 2, starting from 18 mg (37 μmole) of compound A described in Example 9, 11 mg (22 μmole, 59%) of compound A in the title, respectively, starting from

15 mg (31 μmole of compound B, 9 mg (18 μmole, 58%) of compound B in the title are obtained.

Example 11

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(3-N-oxido-2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

Analogously to Example 2, 10 mg (19 μmole) of the compound A prepared according to Example 2 is reacted at 23°C and, after work-up and purification, 3.5 mg (6.5 μmole, 34%) of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.90 (3H), 1.03 (3H), 1.07 (3H), 1.10-2.03 (9H), 1.31 (3H), 1.43 (3H), 2.03 (1H), 2.09 (3H), 2.19-2.26 (2H), 2.52 (1H), 2.61 (3H), 2.68-2.81 (2H), 3.34 (1H), 3.65 (1H), 4.59 (1H), 5.39 (1H), 6.61 (1H), 6.81 (1H), 7.08 (1H) ppm.

Example 12

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-benzyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethylcyclohexadec-13-ene-2,6-dione

Example 12a

(4S)-4-((3RS)-2-Methyl-3-hydroxy-5-phenyl-pent-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 11, 2.97 g (15.9 mmole) of the compound prepared according to Example 1k is reacted using phenethylmagnesium bromide and, after work-up and purification, 327 g (11.2 mmole, 70%) of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.72 + 0.88 (3H), 0.89 + 0.93 (3H), 1.33 (1H), 1.39 + 1.42 (3H), 1.47 + 1.50 (3H), 1.58-1.93 (3H), 2.61 (1H), 3.00 (1H), 3.48-3.60 (1H), 3.72-4.03 (4H), 7.13-7.35 (5H) ppm.

Example 12b

(4S)-4-(2-Methyl-3-oxo-5-phenyl-pent-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1m, 2.71 g (9.3 mmole) of the compound prepared according to Example 12a is reacted, and, after work-up and purification, 2.35 g (8.1 mmole, 87%) of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.03 (3H), 1.12 (3H), 1.28 (1H), 1.31 (3H), 1.38 (3H), 1.60 (1H), 2.77-2.92 (4H), 3.83 (1H), 3.93 (1H), 4.02 (1H), 7.12-7.22 (3H), 7.22-7.32 (2H) ppm.

Example 12c

(4S(4R,5S,6S,10RS))-4-(2,6-Dimethyl-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-benzyl-5-hydroxy-3-oxo-undec-2-yl)-2,2-dimethyl-[1,3]dioxane (A) and (4S(4S,5R,6S,10RS))-4-(2,6-dimethyl-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-benzyl-5-hydroxy-3-oxo-undec-2-yl)-2,2-dimethyl-[1,3]dioxane (B)

In analogy to Example 1ak, 2.34 g (8.06 mmole) of the compound prepared according to Example 12b is reacted, and, after work-up and purification, 2.91 g (4.32 mmole, 54%) of compound A in the title as well as 1.72 g (2.55 mmole, 32%) of compound B in the title are isolated, each as a colorless oil.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.38 (3H), 0.83-1.82 (31H), 2.66-3.02 (3H), 3.47 (1H), 3.58 (1H), 3.74-3.94 (4H), 7.05-7.28 (5H), 7.31-7.46 (6H), 7.61-7.72 (4H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.78 (3H), 0.82-1.66 (21H), 0.98 (3H), 1.29 (3H), 1.36 (3H), 2.78 (1H), 2.94 (1H), 3.05 (1H), 3.44 (1H), 3.54 (1H), 3.72-3.91 (4H), 7.04-7.29 (5H), 7.31-7.48 (6H), 7.63-7.75 (5H) ppm.

Example 12d

(4S(4R,5S,6S,10RS))-4-(2,6-Dimethyl-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-benzyl-3-oxo-5-(tetrahydropyran-2-yloxy)-undec-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1a, 2.90 g (4.4 mmole) of compound A prepared according to Example 12c is reacted, and, after work-up and purification, 3.18 g (4.2 mmole, 95%) of the compound in the title are obtained as a colorless oil.

Example 12e

(4S(4R,5S,6S,10RS))-4-(2,6-Dimethyl-4-benzyl-10-hydroxy-3-oxo-5-(tetrahydropyran-2-yloxy)-undec-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1i, 3.18 g (4.20 mmole) of the compound prepared according to Example 12d is reacted, and, after work-up and purification, 1.39 g (2.68 mmole, 64%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.28 + 0.47 + 0.49 (3H), 0.92-1.14 (7H), 1.14-1.95 (24H), 2.79 + 2.99-3.13 (2H), 3.34-4.27 (8H), 4.45 + 4.56 (1H), 7.05-7.29 (5H) ppm.

Example 12f

(4S(4R,5S,6S))-4-(2,6-Dimethyl-4-benzyl-3,10-dioxo-5-(tetrahydropyran-2-yloxy)-undec-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1m, 1.39 g (2.68 mmole) of the compound prepared according to Example 12e is reacted, and, after work-up and purification, 1.18 g (2.28 mmole, 85%) of the compound in the title is isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.26 + 0.47 (3H), 0.96-1.11 (7H), 1.27 + 1.31 (3H), 1.39 + 1.41 (3H), 1.20-1.90 (12H), 2.15 (3H), 2.45 (2H), 2.79 + 2.97-3.12 (2H), 3.36-4.07 (6H), 4.15 + 4.21 (1H), 4.43 + 4.54 (1H), 7.08-7.28 (5H) ppm.

Example 12g

(4S(4R,5S,6S,10E/Z,13S,14E))-4-(13-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-benzyl-15-(2-methyl-4-thiazolyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-2,6,10,14-tetramethyl-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1ao, 477 mg (923 μmole) of the compound prepared according to Example 12f is reacted using n-butyllithium as base, and, after work-up and purification, 367 mg (393 μmole, 43%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.23 + 0.46 (3H), 0.92-1.10 (19H), 1.10-1.92 (22H), 1.99 (3H), 2.13-2.40 (2H), 2.70 (3H), 2.80 + 2.94-3.14 (2H), 3.35-4.25 (6H), 4.47 + 4.53 (1H), 4.98 (1H), 6.22 (1H), 6.77 (1H), 7.07-7.24 (5H), 7.25-7.45 (6H), 7.60-7.73 (4H) ppm.

Example 12h

(4S(4R,5S,6S,10E/Z,13S,14E))-4-(4-benzyl-13-hydroxy-15-(2-methyl-4-thiazolyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-2,6,10,14-tetramethyl-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1i, 548 mg (586 μmole) of the compound prepared according to Example 12g is reacted and, after work-up and purification, 330 mg (474 μmole, 81%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.25 + 0.46 (3H), 0.92-1.10 (6H), 1.10-1.90 (13H), 1.28 + 1.32 (3H), 1.39 + 1.41 (3H), 1.68 + 1.74 (3H), 1.99-2.13 (2H), 2.06 (3H), 2.36 (2H), 2.71 (3H), 2.81 + 3.00-3.14 (2H), 3.37-4.26 (9H), 4.48 + 4.57 (1H), 5.20 (1H), 6.58 (1H), 6.94 (1H), 7.08-7.26 (5H) ppm.

Example 12i

3S,6R,7S,8S,12E/Z,15S,16E)-6-benzyl-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12-16-pentamethyl-heptadeca-12,16-diene-1,3,7,15-tetraol

In analogy to Example 1f, 330 mg (474 μmole) of the compound prepared according to Example 12h is reacted, and, after work-up and purification, 224 mg (392 μmole, 83%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.40 (3H), 0.93-1.04 (6H), 1.08-1.87 (8H), 1.63 + 1.71 (3H), 1.92-2.11 (5H), 2.33 (2H), 2.67-3.06 (3H), 2.72 (3H), 3.11 (1H), 3.23-3.50 (2H), 3.54 (1H), 3.65-3.92 (3H), 4.13 (1H), 5.18 (1H), 6.53 (1H), 6.94 (1H), 7.06-7.29 (5H) ppm.

Example 12k

(3S,6R,7S,8S,12E/Z,15S,16E)-6-benzyl-17-(2-methyl-4-thiazolyl)-4,4,8,12,16-pentamethyl-1,3,7,15-tetrakis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dien-5-one

In analogy to Example 1aq, 224 mg (392 μmole) of the compound prepared according to Example 12i is reacted, and, after work-up and purification, 323 mg (314 μmole, 80%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.03-0.12 (24H), 0.79-1.73 (53H), 1.61 + 1.69 (3H), 1.91-2.07 (2H), 2.00 (3H), 2.26 (2H), 2.71 (3H), 2.86 (1H), 2.98 (1H), 3.33-3.55 (2H), 3.66 (1H), 3.80 (1H), 4.10 (1H), 5.17 (1H), 6.47 (1H), 6.91 (1H), 7.06-7.29 (H) ppm.

Example 12l

(3S,6R,7S,8S,12E/Z,15S,16E)-6-benzyl-1-hydroxy-17-(2-methyl-4-thiazolyl)-4,4,8,12,16-pentamethyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dien-5-one

In analogy to Example 1ar, 432 mg (420 μmole) of the compound prepared according to Example 12k are reacted, and, after work-up and purification, 264 mg (289 μmole, 69%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.03-0.12 (18H), 0.53 (1H), 0.78-1.40 (41H), 1.62 + 1.71 (3H), 1.42-1.81 (2H), 2.00 (3H), 1.92-2.10 (2H), 2.27 (2H), 2.70 (3H), 2.852 (1H), 3.09 (1H), 3.30 (2H), 3.40 (1H), 3.70 (1H), 3.81 (1H), 4.11 (1H), 5.17 (1H), 6.46 (1H), 6.91 (1H), 7.11-7.30 (5H) ppm.

Example 12m

(3S,6R,7S,8S,12E/Z,15S,16E)-6-benzyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-methyl-4-thiazolyl)-5-oxo-heptadeca-12,16-dienoic acid

In analogy to Example 1k, 264 mg (289 μmole) of the compound prepared according to Example 12l is reacted, and, after work-up, 255 mg (279 μmole, 97%) of the compound in the title are isolated as a colorless oil, which is reacted further without purification.

Example 12n

(3S,6R,7S,8S,12Z,15S,16E)-6-benzyl-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12,16-pentamethyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dienoic acid (A) and

(3S,6R,7S,8S,12E,15S,16E)-6-benzyl-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12,16-pentamethyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dienoic acid (B)

In analogy to Example 1at, 255 mg (279 μmole) of the compound prepared according to Example 12m are reacted, and, after work-up and purification, 61 mg (66 μmole, 24%) of compound A in the title are isolated as a colorless solid, as well as 54 mg (58 μmole, 21%) of compound B in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$ of A: δ = -0.07-0.18 (18H), 0.60 (3H), 0.78 (3H), 0.82 (9H), 0.89 (9H), 0.92 (9H), 1.07 (3H), 1.72 (3H), 1.95 (3H), 0.74-2.33 (12H), 2.69 (3H), 2.91 (1H), 3.03 (1H), 3.41 (1H), 3.62 (1H), 4.20 (1H), 4.30 (1H), 5.23 (1H), 6.72 (1H), 6.96 (1H), 7.05-7.29 (5H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = -0.08-0.14 (18H), 0.72 (3H), 0.82 (3H), 0.85 (9H), 0.90 (9H), 0.93 (9H), 0.98 (3H), 1.60 (3H), 0.65-2.08 (9H), 1.96 (3H), 2.12 (1H), 2.29 (2H), 2.71 (3H), 2.92 (2H), 3.47 (1H), 3.69 (1H), 4.09 (1H), 4.21 (1H), 5.12 (1H), 6.49 (1H), 6.95 (1H), 7.06-7.30 (5H) ppm.

Example 12o

(3S,6R,7S,8S,12Z,15S,16E)-6-benzyl-15-hydroxy-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12,16-pentamethyl-3,7-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dienoic acid

In analogy to Example 1i, 61 mg (66 μmole) of compound A, prepared according to Example 12n, are reacted at 23°C, and, after work-up and purification, 33 mg (41 μmole, 61%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.11 (3H), -0.08-0.05 (9H), 0.80 (9H), 0.88 (9H), 0.91 (3H), 0.94 (3H), 0.99 (3H), 1.72 (3H), 1.98 (3H), 0.77-2.22 (12H), 2.69 (3H), 2.70-2.91 (2H), 3.39 (1H), 3.62 (1H), 4.18 (1H), 4.33 (1H), 4.43-5.73 (1H), 5.13 (1H), 6.68 (1H), 6.91 (1H), 7.05-7.26 (5H) ppm.

Example 12p

(4S,7R,8S,9S,13Z,16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-7-benzyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1aw, 33 mg (40 μmole) of the compound prepared according to Example 12o are reacted, and, after work-up and purification, 17 mg (21 μmole, 53%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.06 (3H), 0.00 (3H), 0.07 (3H), 0.09 (3H), 0.98 (3H), 1.71 (3H), 2.10 (3H), 0.70-2.48 (34H), 2.63 (1H), 2.71 (3H), 2.81 (2H), 3.23 (1H), 3.76 (1H), 4.17 (1H), 5.13 (2H), 6.56 (1H), 6.95 (1H), 7.06-7.32 (5H) ppm.

Example 12

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-benzyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1, 12.2 mg (9.7 μmole) of the compound prepared according to Example 12p are reacted, and, after work-up and purification, 5.0 mg (8.8 μmole, 91%) of the compound in the title are isolated as a colorless oil.

^{H}-NMR ($CDCl_3$): δ = 0.61 (3H), 0.83 (3H), 1.11 (3H), 1.22-2.00 (5H), 1.71 (3H), 2.05 (3H), 2.19-2.49 (5H), 2.61 (1H), 2.66 (3H), 2.89 (1H), 3.03 (1H), 3.59 (1H), 3.67 (1H), 4.21 (1H), 5.10 (1H), 5.24 (1H), 6.53 (1H), 6.92 (1H), 7.07-7.31 (5H) ppm.

Example 13

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-7-benzyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

Example 13a

(3S,6R,7S,8S,12E,15S,16E)-6-benzyl-15-hydroxy-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12,16-pentamethyl-3,7-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dienoic acid

In analogy to Example 1i, 47 mg (51 μmole) of compound B, prepared according to Example 12n, are reacted at 23°C, and, after work-up and purification, 22 mg (27 μmole, 53%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.08 (3H), -0.03-0.09 (9H), 0.82 (9H), 0.89 (12H), 0.97 (6H), 1.64 (3H), 2.02 (3H), 0.78-2.10 (9H), 2.27-2.46 (2H), 2.70 (3H), 2.82 (2H), 2.92-3.34 (2H), 3.42 (1H), 3.67 (1H), 4.19 (1H), 4.32 (1H), 5.28 (1H), 6.63 (1H), 6.92 (1H), 7.02-7.27 (5H) ppm.

Example 13b

(4S,7R,8S,9S,13E,16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-7-benzyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1aw, 22 mg (27 μmole) of the compound prepared according to Example 13a are reacted, and, after work-up and purification, 12 mg (15 μmole, 56%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.04 (3H), 0.06 (6H), 0.12 (3H), 0.80 (3H), 0.88 (9H), 0.90 (9H), 0.96 (3H), 1.08 (3H), 1.64 (3H), 0.74-1.72 (4H), 1.80-2.27 (5H), 2.09 (3H), 2.33 (1H), 2.53-2.82 (2H), 2.70 (3H), 2.96 (1H), 3.20 (1H), 3.74 (1H), 4.15 (1H), 5.19-5.32 (2H), 6.47 (1H), 6.90 (1H), 7.07-7.31 (5H) ppm.

Example 13

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-7-benzyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1, 12 mg (15 μmole) of the compound prepared according to Example 13b are reacted, and, after work-up and purification, 6.0 mg (11 μmole, 69%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.69 (3H), 0.72 (3H), 0.89 (1H), 1.08 (3H), 1.38-1.69 (3H), 1.61 (3H), 1.90-2.12 (2H), 2.02 (3H), 2.19 (1H), 2.25-2.44 (3H), 2.54 (1H), 2.69 (3H), 2.79 (1H), 2.99 (1H), 3.73 (2H), 4.25-4.39 (2H), 4.66 (1H), 5.03 (1H), 5.34 (1H), 6.52 (1H), 6.97 (1H), 7.04-7.29 (5H) ppm.

Example 14

(1S,3S(E),7S,10R,11S,12S,16R)-10-benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and

(1R,3S(E),7S,10R,11S,12S,16S)-10-benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B)

The solution of 4.0 mg (7.0 μmole) of the compound prepared according to Example 12 in 0.1 mL of acetonitrile is treated with 38 μL of a 1 M solution of sodium ethylenediamine-tetraacetate, cooled to 0°C and treated with 67 μL of 1,1,1-trifluoroacetone as well as with a mixture of 21 mg of oxone and 4.5 mg of sodium hydrogen carbonate. The mixture is allowed to react for 5 hours, is poured into sodium thiosulfate solution and extracted several times with ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution and the residue obtained after filtration and removal of the solvent is purified by chromatography on an analytical thin-layer plate. A mixture of n-hexane and ethyl acetate is used as solvent. Thus, 2.2 mg (3.8 μmole, 54%) of compound A in the title as well as 0.3 mg (0.5 μmole, 7%) of compound B in the title are isolated, each as a colorless oil.

^{1}H-NMR ($CDCl_3$ of A: δ = 0.67 (3H), 0.80 (3H), 1.07 (3H), 1.29 (3H), 1.35-2.06 (9H), 2.09 (3H), 2.33 (1H), 2.49 (1H), 2.68 (3H), 2.72-2.85 (2H), 3.04 (1H), 3.40 (1H), 3.62 (1H), 3.77 (1H), 4.22 (1H), 4.51 (1H), 5.47 (1H), 6.51 (1H), 6.95 (1H), 7.06-7.30 (5H) ppm.

^{1}H-NMR ($CDCl_3$ of B: δ = 0.68 (3H), 0.76 (3H), 0.86 (1H), 1.07 (3H), 1.23-2.13 (7H), 1.30 (3H), 2.08 (3H), 2.30-2.49 (2H), 2.70 (3H), 2.87-3.11 (3H), 3.28 (2H), 3.57 (1H), 3.93 (1H), 4.21 (1H), 4.54-5.73 (1H), 5.58 (1H), 6.58 (1H), 6.97 (1H), 7.07-7.31 (5H) ppm.

Example 15

(1S,3S(E),7S,10R,11S,12S,16S)-10-benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and

(1R,3S(E),7S,10R,11S,12S,16R)-10-benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B)

In analogy to Example 14, 3.1 mg (5.4 μmole) of the compound obtained according to Example 13 is reacted, and, after work-up and purification, 0.7 mg (1.2 μmole, 22%) of compound A or B in the title, as well as 0.6 mg (1.0 μmole, 19%) of compound B or A in the title are isolated as colorless oils.

^{1}H-NMR ($CDCl_3$) of A or B: δ = 0.76 (3H), 0.88 (3H), 1.02 (3H), 1.24 (1H), 1.30 (3H), 1.38-1.78 (5H), 1.92-2.13 (3H), 2.07 (3H), 2.44 (2H), 2.70 (3H), 2.78-2.87 (2H), 3.04 (1H), 3.60 (1H), 3.71-3.80 (2H), 4.01 (1H), 4.28 (1H), 5.45 (1H), 6.62 (1H), 6.99 (1H), 7.11-7.31 (5H) ppm.

^{1}H-NMR ($CDCl_3$) of B or A: δ = 0.70 (3H), 0.76 (3H), 1.06 (3H), 1.19-1.64 (5H), 1.22 (3H), 1.80 (1H), 1.90-2.12 (3H), 2.07 (3H), 2.46 (2H), 2.69 (3H), 2.79 (1H), 2.92 (1H), 3.08 (1H), 3.32 (1H), 3.57 (1H), 3.62 (1H), 3.71 (1H), 4.12 (1H), 5.42 (1H), 6.54 (1H), 6.96 (1H), 7.06-7.31 (5H) ppm.

Example 16

(4S,7S,8R,9S,13Z,16S(E))-4,8-Dihydroxy-7-benzyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

Example 16a

(4S(4S,5R,6S,10RS))-4-(2,6-Dimethyl-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-benzyl-3-oxo-5-(tetrahydropyran-2-yloxy)-undec-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1a, 1.71 g (2.59 mmole) of compound B prepared according to Example 12c are reacted, and, after work-up and purification, 1,51 g (1.99 mmole, 77%) of the compound in the title are isolated as a colorless oil.

Example 16b

(4S(4S,5R,6S,10RS))-4-(2,6-Dimethyl-4-benzyl-10-hydroxy-3-oxo-5-(tetrahydropyran-2-yloxy)-undec-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1i, 1.51 g (1.99 mmole) of the compound prepared according to Example 16a are reacted, and, after work-up and purification, 855 mg (1.65 mmole, 83%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.88 + 0.92 (3H), 0.92-1.95 (32H), 2.82-3.10 (2H), 3.32-3.59 (2H), 3.71-3.98 (5H), 4.43-4.59 (1H), 7.11-7.31 (5H) ppm.

Example 16c

(4S(4S,5R,6S))-4-(2,6-Dimethyl-4-benzyl-3,10-dioxo-5-(tetrahydropyran-2-yloxy)-undec-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1m, 850 mg (1.64 mmole) of the compound prepared according to Example 16b are reacted, and, after work-up and purification, 741 mg (1.43 mmole, 88%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.84 + 0.90 (3H), 0.95 + 1.05 (3H), 0.97 (3H), 1.8-1.88 (19H), 2.15 (3H), 2.42 (2H), 2.79-3.08 (2H), 3.31-3.57 (2H), 3.69-3.96 (5H), 4.43 + 4.52 (1H), 7.10-7.29 (5H) ppm.

Example 16d

(4S(4S,5R,6S,10E/Z,13S,14E))-4-(13-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-benzyl-15-(2-methyl-4-thiazolyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-2,6,10,14-tetramethyl-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1ao, 737 mg (1.43 mmole) of the compound prepared according to Example 16c are reacted using n-butyllithium as base, and, after work-up and purification, 491 mg (525 μmole, 37%) of the compound in the title are isolated as a colorless oil.

Example 16e

(4S(4S,5R,6S,10E/Z,13S,14E))-4-(4-benzyl-13-hydroxy-15-(2-methyl-4-thiazolyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-2,6,10,14-tetramethyl-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1i, 1.09 g (1.17 mmole) of the compound prepared according to Example 16d are reacted, and, after work-up and purification, 677 mg (973 μmole, 83%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.78-2.12 (31H), 1.67 + 1.73 (3H), 2.06 (3H), 2.36 (2H), 2.71 (3H), 2.81-3.08 (2H), 3.30-3.52 (2H), 3.69-3.96 (5H), 4.14 (1H), 4.43 + 4.51 (1H), 5.20 (1H), 6.57 (1H), 6.95 (1H), 7.08-7.30 (5H) ppm.

Example 16f

(3S,6S,7R,8S,12E/Z,15S,16E)-6-benzyl-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12,16-pentamethyl-heptadeca-12,16-diene-1,3,7,15-tetraol

In analogy to Example 1f, 675 mg (970 μmole) of the compound prepared according to Example 16e are reacted, and, after work-up and purification, 495 mg (866 μmole, 89%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.73-0.86 (6H), 0.96-1.10 (3H), 1.21-1.79 (7H), 1.67 + 1.76 (3H), 1.98-2.17 (5H), 2.28-2.50 (3H), 2.70 (3H), 2.85 (1H), 2.97 (1H), 3.09 (1H), 3.40-3.87 (7H), 4.16 (1H), 5.27 (1H), 6.51 + 6.57 (1H), 6.94 (1H), 7.07-7.30 (5H) ppm.

Example 16g

(3S,6S,7R,8S,12E/Z,15S,16E)-6-benzyl-17-(2-methyl-4-thiazolyl)-4,4,8,12,16-penta-methyl-1,3,7,15-tetrakis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dien-5-one

In analogy to Example 1aq, 337 mg (589 μmole) of the compound prepared according to Example 16f are reacted, and, after work-up and purification, 444 mg (432 μmole, 73%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.08-0.13 (24H), 0.42 (3H), 0.79-1.03 (42H), 1.11-1.73 (8H), 1.60 + 1.67 (3H), 1.90-2.08 (4H), 2.26 (2H), 2.71 (3H), 2.91 (2H), 3.22 (1H), 3.50-3.72 (3H), 3.85 (1H), 4.09 (1H), 5.16 (1H), 6.46 (1H), 6.91 (1H), 7.07-7.27 (5H) ppm.

Example 16h

(3S,6S,7R,8S,12E/Z,15S,16E)-6-benzyl-1-hydroxy-17-(2-methyl-4-thiazolyl)-4,4,8,12,16-pentamethyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dien-5-one

In analogy to Example 1ar, 444 mg (432 μmole) of the compound prepared according to Example 16g are reacted, and, after work-up and purification, 272 mg (297 μmole, 69%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.07-0.18 (18H), 0.48 (3H), 0.79-1.72 (40H), 1.61 + 1.68 (3H), 1.81 (1H), 1.90-2.09 (5H), 2.26 (2H), 2.70 (3H), 2.86-3.04 (2H), 3.23 (1H), 3.59 (2H), 3.70 (1H), 3.91 (1H), 4.10 (1H), 5.16 (1H), 6.44 (1H), 6.91 (1H), 7.08-7.29 (5H) ppm.

Example 16i

(3S,6S,7R,8S,12E/Z,15S,16E)-6-benzyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-methyl-4-thiazolyl)-5-oxo-heptadeca-12,16-dienoicacid

In analogy to Example 1k, 272 mg (297 μmole) of the compound prepared according to Example 16h are reacted, and, after work-up, 264 mg (289 μmole, 97%) of the compound in the title are isolated as a colorless oil, which is reacted further without purification.

Example 16k

(3S,6S,7R,8S,12Z,15S,16E)-6-benzyl-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12,16-pentamethyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dienoic acid (A) and

(3S,6S,7R,8S,12E,15S,16E)-6-benzyl-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12,16-pentamethyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dienoicacid (B)

In analogy to Example 1at, 264 mg (289 μmole) of the compound prepared according to Example 16i are reacted, and, after work-up and purification, 87 mg (94 μmole, 32%) of compound A in the title, as well as 67 mg (73 μmole, 25%) of compound B in the title are isolated as colorless oils.

^{1}H-NMR ($CDCl_3$) of A: δ = -0.09 (3H), -0.02-0.13 (15H), 0.69 (3H), 0.80-1.48 (32H), 1.03 (3H), 1.63-1.79 (1H), 1.68 (3H), 2.00 (3H), 1.91-2.09 (2H), 2.12-2.33 (3H), 2.72 (3H), 2.77-3.20 (6H), 3.31 (1H), 3.70 (1H), 4.10 (1H), 4.43 (1H), 5.16 (1H), 6.47 (1H), 6.91 (1H), 7.08-7.29 (5H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = -0.10 (3H), -0.03-0.17 (15H), 0.68 (3H), 0.80-1.50 (33H), 1.02 (3H), 1.61 (3H), 1.71 (2H), 1.88-2.07 (2H), 2.00 (3H), 2.11-2.68 (4H), 2.71 (3H), 2.86 (2H), 3.30 (1H), 3.69 (1H), 3.75-4.08 (1H), 4.11 (1H), 4.43 (1H), 5.16 (1H), 6.47 (1H), 6.91 (1H), 7.08-7.30 (5H) ppm.

Example 16l

(3S,6S,7R,8S,12Z,15S,16E)-6-benzyl-15-hydroxy-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12,16-pentamethyl-3,7-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dienoic acid

In analogy to Example 1i, 87 mg (94 μmole) of compound A, prepared according to Example 16k, are reacted at 23°C, and, after work-up and purification, 76 mg (93 μmole, 99%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.03-0.13 (12H), 0.52 (3H), 0.78-180 (28H), 1.73 (3H), 1.91-2.17 (2H), 2.00 (3H), 2.21 (2H), 2.34 (2H), 2.69-3.01 (3H), 2.73 (3H), 3.19 (1H), 3.31 (1H), 3.74 (1H), 4.13 (1H), 4.28-5.68 (1H), 4.36 (1H), 5.18 (1H), 6.62 (1H), 6.97 (1H), 7.08-7.31 (5H) ppm.

Example 16m

(4S,7S,8R,9S,13Z,16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-7-benzyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1aw, 76 mg (93 μmole) of the compound prepared according to Example 16l are reacted, and, after work-up and purification, 68 mg (85 μmole, 92%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.02 (3H), 0.01 (3H), 0.16 (3H), 0.30 (3H), 0.54 (3H), 0.64 (3H), 0.85 (9H), 0.97 (9H), 0.99 (3H), 0.80-1.75 (5H), 1.69 (3H), 1.89 (1H), 1.98-2.31 (3H), 2.13 (3H), 2.37 (1H), 2.52 (1H), 2.70 (1H), 2.72 (3H), 3.10 (1H), 3.46 (1H), 3.96 (1H), 4.05 (1H), 5.10 (1H), 5.15 (1H), 6.48 (1H), 7.02 (1H), 7.09-7.31 (5H) ppm.

Example 16

(4S,7S,8R,9S,13Z,16S(E))-4,8-Dihydroxy-7-benzyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1, 10 mg (13 µmole) of the compound prepared according to Example 12p are reacted, and, after work-up and purification, 6.3 mg (11 µmole, 89%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.47 (3H), 0.84 (1H), 0.97 (3H), 1.04 (3H), 1.22-1.70 (4H), 1.76 (3H), 1.94 (1H), 1.93 (3H), 2.22-2.49 (4H), 2.61-2.77 (1H), 2.71 (3H), 2.83 (1H), 2.90 (1H), 3.02 (1H), 3.08 (1H), 3.59 (1H), 3.62 (1H), 4.18 (1H), 5.19 (1H), 5.53 (1H), 6.50 (1H), 6.96 (1H), 7.08-7.31 (5H) ppm.

Example 17

(4S,7S,8R,9S,13E,16S(E))-4,8-Dihydroxy-7-benzyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

Example 17a

(3S,6S,7R,8S,12E,15S,16E)-6-benzyl-15-hydroxy-17-(2-methyl-4-thiazolyl)-5-oxo-4,4,8,12,16-pentamethyl-3,7-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dienoic acid

In analogy to Example 1i, 67 mg (72 µmole) of compound B, prepared according to Example 16k, are reacted at 23°C, and, after work-up and purification, 57 mg (70 µmole, 97%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.06-0.13 (12H), 0.47 (3H), 0.77-1.76 (28H), 1.64 (3H), 1.90-2.07 (2H), 2.00 (3H), 2.28 (2H), 2.39 (2H), 2.66-2.89 (2H), 2.73 (2H), 2.91-3.05 (3H), 3.19 (1H), 3.29 (1H), 3.76 (1H), 4.20 (1H), 4.36 (1H), 5.16 (1H), 6.58 (1H), 6.94 (1H), 7.07-7.31 (5H) ppm.

Example 17b

(4S,7S,8R,9S,13E,16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-7-benzyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1aw, 57 mg (70 μmole) of the compound prepared according to Example 17a are reacted, and, after work-up and purification, 32 mg (40 μmole, 57%) of the compound in the title are isolated as a colorless solid.

^{1}H-NMR ($CDCl_3$): δ = 0.07 (9H), 0.23 (3H), 0.53 (3H), 0.72 (3H), 0.88 (9H), 0.93 (9H), 0.98 (3H), 1.08-1.30 (2H), 1.39 (1H), 1.48-1.86 (3H), 1.61 (3H), 2.10 (3H), 2.07-2.27 (2H), 2.31-2.58 (3H), 2.63-2.78 (1H), 2.71 (3H), 3.08 (1H), 3.41 (1H), 3.82 (1H), 4.19 (1H), 5.08 (1H), 5.15 (1H), 6.51 (1H), 7.02 (1H), 7.08-7.30 (5H) ppm.

Example 17

(4S,7S,8R,9S,13E,16S(E))-4,8-Dihydroxy-7-benzyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1, 32 mg (40 μmole) of the compound prepared according to Example 17b are reacted, and, after work-up and purification, 16.6 mg (29 μmole, 73%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.35 (3H), 0.91 (3H), 0.93 (3H), 1.61 (3H), 0.83-1.72 (5H), 1.94-2.20 (2H), 2.09 (3H), 2.32 (1H), 2.46 (1H), 2.51 (2H), 2.69 (3H), 2.90-3.02 (3H), 3.13 (1H), 3.55-3.68 (2H), 4.23 (1H), 5.11 (1H), 5.43 (1H), 6.47 (1H), 6.92 (1H), 7.07-7.31 (5H) ppm.

Example 18

(1S,3S(E),7S,10S,11R,12S,16R)-10-benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and

(1R,3S(E),7S,10S,11R, 12S, 16S)-10-benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B)

In analogy to Example 14, 1.4 mg (2.5 μmole) of the compound prepared according to Example 16 are reacted, and, after work-up and purification, 0.3 mg (0.5 μmole, 21%) of compounds A and B in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.27 (3H), 0.98 (3H), 1.08 (3H), 1.23 (3H), 1.15-2.46 (10H), 2.19 (3H), 2.71 (3H), 2.82 (1H), 291 (1H), 2.95 (1H), 3.10 (1H), 3.47 (1H), 3.95 (1H), 4.12 (1H) 4.42 (1H), 4.70-5.30 (1H), 5.60 (1H), 6.65 (1H), 7.00 (1H), 7.12-7.32 (5H) ppm.

Example 19

(1S,3S(E),7S,10S,11R,12S,16S)-10-benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and (1R,3S(E),7S,10S,11R,12S,16R)-10-benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B)

In analogy to Example 14, 7.4 mg (13 μmole) of the compound prepared according to Example 17 are reacted, and, after work-up and purification, 1.9 mg (3.3 μmole, 25%) of compound A in the title, as well as 1.7 mg (2.9 μmole, 22%) of compound B in the title are each isolated as a colorless oil.

^{1}H-NMR($CDCl_3$) of A: δ = 0.40 (3H), 0.89 (3H), 0.97 (3H), 1.08-1.77 (6H), 1.22 (3H), 1.90-2.07 (3H), 2.08 (3H), 2.38 (1H), 2.57 (1H), 2.70 (3H), 2.83 (1H), 2.92-3.06 (3H), 3.19 (1H), 3.54 (1H), 3.77 (1H), 4.19 (1H), 5.53 (1H), 6.52 (1H), 6.97 (1H), 7.08-7.31 (5H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.17 (3H), 0.89 (3H), 1.00 (3H), 1.21-1.97 (8H), 1.28 (3H), 2.06 (1H), 2.10 (3H), 2.27-2.44 (3H), 2.71 (3H), 2.90 (1H), 2.99-3.11 (2H), 3.36 (1H), 3.96 (1H), 4.20 (1H), 4.29 (1H), 5.77 (1H), 6.57 (1H), 6.98 (1H), 7.08-7.31 (5H) ppm.

Example 20

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione

Example 20a

(5E,3S)-[3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-pyridyl)-pent-4-en-1-yl]-triphenylphosphonium iodide

In analogy to Example 7a to 7d, using diethyl(2-pyridyl)methanephosphonate, the compound in the title is obtained as a crystalline solid.

^{1}H-NMR ($CDCl_3$): δ = 1.08 (9H), 1.70-1.95 (2H), 1.99 (1H), 3.00 (1H), 3.31 (1H), 4.59 (1H), 6.68 (1H), 7.10 (1H), 7.18-7.46 (8H), 7.50-7.74 (18H), 7.74-7.87 (3H), 8.57 (1H) ppm.

Example 20b

(4S(4R,5S,6S,10E/Z,13S,14E))-4-(13-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-15-(2-pyridyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-2,4,6,10,14-pentamethyl-pentadeca-10,14-dien-2yl)-2,2-dimethyl-[1,3]dioxane

Analogously to Example 1ao, 2.9 g (6.58 mmole) of the compound prepared in analogy to Example 1l (reaction with ethylmagnesium bromide) to 1an, (4S(4R,5S,6S))-4-(3,10-dioxo-2,4,6-trimethyl-5-(tetrahydropyran-2-yloxy)-undec-2-yl)-2,2-dimethyl-[1,3]dioxane, are reacted with 8.0 g (9.95 mmole) of the compound described in Example 20a and 7.54 mL of a 1.6 M solution of n-butyllithium in n-hexane. In addition to the starting material, 1.71 g (2.0 mmole, 31%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.84-0.98 (3H), 0.99-1.97 (42H), 2.01 (3H), 2.29 (2H), 3.22 (1H), 3.41 (1H), 3.58-4.01 (4H), 4.07-4.22 (2H), 4.47 + 4.51 (1H), 5.01 (1H), 6.24 (1H), 7.07 (1H), 7.22-7.46 (7H), 7.52-7.75 (5H), 8.57 (1H) ppm.

Example 20c

(4S(4R,5S,6S,10E/Z,13S,14E))-4-(13-Hydroxy-15-(2-pyridyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-2,4,6,10,14-pentamethyl-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1i, 1.76 g (2.11 mmole) of the compound prepared according to Example 20b are reacted, and, after work-up and purification, 1.17 g (1.95 mmole, 93%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.88-2.13 (37H), 2.09 (3H), 2.39 (2H), 3.26 (1H), 3.44 (1H), 3.75-4.02 (3H), 4.08-4.22 (2H), 4.48 + 4.55 (1H), 5.21 (1H), 6.60 (1H), 7.10 (1H), 7.25 (1H), 7.64 (1H), 8.60 (1H) ppm.

Example 20d

(3S,6R,7S,8S,12E/Z,15S,16E)-1,3,7,15-Tetrahydroxy-4,4,6,8,12,16-hexamethyl-17-(2-pyridyl)-heptadeca-12,16-dien-5-one

In analogy to Example 1f, 1.17 g (1.95 mmole) of the compound prepared according to Example 20c are reacted using p-toluenesulfonic acid monohydrate and, after work-up and purification, 852 mg (1.79 mmole, 92%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.83 + 0.88 (3H), 1.06 (3H), 1.12 (3H), 1.22 (3H), 1.63 + 1.72 (3H), 0.98-1.82 (7H), 1.96-2.21 (3H), 2.07 (3H), 2.39 (2H), 2.90-3.80 (2H), 3.28 (1H),

3.32-3.48 (2H), 3.89 (2H), 4.06 (1H), 4.18 (1H), 5.20 (1H), 6.59 (1H), 7.11 (1H), 7.28 (1H), 7.64 (1H), 8.59 (1H) ppm.

Example 20e

(3S,6R,7S,8S,12E/Z,15S,16E)-1,3,7,15-Tetrakis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-17-(2-pyridyl)-heptadeca-12,16-dien-5-one

In analogy to Example 1aq, 847 mg (1.78 mmole) of the compound prepared according to Example 20d are reacted, and, after work-up and purification, 1.32 g (1.42 mmole, 80%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.02-0.13 (24H), 0.80-0.97 (39H), 1.02 (3H), 1.04 (3H), 1.21 (3H), 1.59 + 1.68 (3H), 1.08-1.70 (7H), 1.89-2.08 (2H), 2.06 (3H), 2.28 (2H), 3.13 (1H), 3.52-3.74 (2H), 3.77 (1H), 3.89 (1H), 4.11 (1H), 5.18 (1H), 6.48 (1H), 7.08 (1H), 7.21 (1H), 7.62 (1H), 8.60 (1H) ppm.

Example 20f

(3S,6R,7S,8S,12E/Z,15S,16E)-3,7,15-Tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-1-hydroxy-17-(2-pyridyl)-heptadeca-12,16-dien-5-one

In analogy to Example 1ar, 1.32 g (1.42 mmole) of the compound prepared according to Example 20e are reacted, and, after work-up and purification, 1.06 g (1.29 mmole, 91%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.00-0.13 (18H), 0.80-0.97 (30H), 1.06 (6H), 1.00-1.63 (7H), 1.21 (3H), 1.58 + 1.68 (3H), 1.89-2.08 (3H), 2.04 (3H), 2.28 (2H), 3.12 (1H), 3.63 (2H), 3.79 (1H), 4.02-4.16 (2H), 5.18 (1H), 6.48 (1H), 7.08 (1H), 7.21 (1H), 7.61 (1H), 8.60 (1H) ppm.

Example 20g

(3S,6R,7S,8S,12E/Z,15S,16E)-3,7,15-Tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-17-(2-pyridyl)-5-oxo-heptadeca-12,16-dienal

In analogy to Example 1k, 1.14 g (1.39 mmole) of the compound prepared according to Example 20f are reacted, and, after work-up, 1.10 g (1.35 mmole, 97%) of the compound in the title are isolated as a colorless oil, which is reacted further without purification.

Example 20h

(3S,6R,7S,8S,12E,15S,16E)-3,7,15-Tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-17-(2-pyridyl)-5-oxo-heptadeca-12,16-dienoic acid (A) and (3S,6R,7S,8S,12Z,15S,16E)-3,7,15-Tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-17-(2-pyridyl)-5-oxo-heptadeca-12,16-dienoic acid (B)

In analogy to Example 1at, 1.10 g (1.35 mmole) of the compound prepared according to Example 20g are reacted, and, after work-up and purification, 467 mg (0.56 mmole, 42%) of compound B in the title, as well as 374 mg (0.45 mmole, 33%) of compound A in the title are isolated as colorless oils.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.00-0.19 (18H), 0.85 (3H), 0.90 (27H), 1.01-1.50 (6H), 1.07 (3H), 1.15 (3H), 1.21 (3H), 1.57 (3H), 1.81-2.08 (1H), 1.96 (3H), 2.24-2.41 (4H), 2.60 (1H), 3.18 (1H), 3.83 (1H), 4.13 (1H), 4.38 (1H), 5.13 (1H), 6.50 (1H), 7.16 (1H), 7.36 (1H), 7.71 (1H), 8.61 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = -0.02-0.17 (18H), 0.80-0.98 (30H), 1.00-1.59 (6H), 1.05 (3H), 1.13 (3H), 1.18 (3H), 1.69 (3H), 1.81-1.98 (1H), 1.91 (3H), 2.10-2.40 (4H), 2.49 (1H), 3.10 (1H), 3.79 (1H), 4.15 (1H), 4.42 (1H), 5.21 (1H), 6.63 (1H), 7.17 (1H), 7.31 (1H), 7.70 (1H), 8.58 (1H) ppm.

Example 20i

(3S,6R,7S,8S,12Z,15S,16E)-3,7-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-15-hydroxy-17-(2-pyridyl)-5-oxo-heptadeca-12,16-dienoic acid

In analogy to Example 1i, 405 mg (0.49 mmole) of compound B prepared according to Example 20h are reacted, and, after work-up and purification, 338 mg (0.47 mmole, 96%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.00-0.15 (12H), 0.80-0.99 (21H), 1.02-1.60 (6H), 1.07 (3H), 1.14 (3H), 1.19 (3H), 1.72 (3H), 1.90-2.08 (1H), 1.99 (3H), 2.17 (1H), 2.31 (1H), 2.38 (2H), 2.49 (1H), 3.00-4.00 (1H), 3.12 (1H), 3.81 (1H), 4.19 (1H), 4.43 (1H), 5.24 (1H), 6.73 (1H), 7.18 (1H), 7.32 (1H), 7.71 (1H), 8.60 (1H) ppm.

Example 20j

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1aw, 287 mg (0.40 mmol) of the compound prepared according to Example 20i are reacted, and, after work-up and purification, 144 mg (0.21 mmole, 51%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.09 (3H), 0.01-0.18 (9H), 0.79-1.32 (4H), 0.85 (9H), 0.94 (9H), 0.98 (3H), 1.10 (3H), 1.14 (3H), 1.20 (3H), 1.46-1.82 (3H), 1.69 (3H), 2.03-2.21 (1H), 2.15 (3H), 2.49 (1H), 2.62-2.88 (2H), 3.03 (1H), 3.90 (1H), 4.05 (1H), 5.02 (1H), 5.19 (1H), 6.58 (1H), 7.11 (1H), 7.27 (1H), 7.65 (1H), 8.61 (1H) ppm.

Example 20

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1, 144 mg (206 μmole) of the compound prepared according to Example 20j are reacted, and, after work-up and purification, 90 mg (191 μmole, 93%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.08 (3H), 1.20 (3H), 1.24-1.43 (4H), 1.38 (3H), 1.67 (3H), 1.60-1.98 (2H), 2.06 (3H), 2.23 (1H), 2.31 (2H), 2.45 (1H), 2.64 (1H), 3.11-3.27 (2H), 3.73 (1H), 4.41 (1H), 4.50-4.77 (1H), 5.09-5.23 (2H), 6.62 (1H), 7.14 (1H), 7.31 (1H), 7.69 (1H), 8.52 (1H) ppm.

Example 21

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and (1R,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B) and (4S,7R,8S,9S,13(Z),16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-N-oxypyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione (C) and (1S,3S(E),7S,10R,11S,12S,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-N-oxypyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (D) and (1R,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-N-oxypyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (E)

In analogy to Example 14, 40 mg (84 μmole) of the compound prepared according to Example 20 is reacted and, after work-up and purification, 8.5 mg (17 μmole, 21%) of compound A in the title, 2.0 mg (4 μmole, 5%) of compound B in the title, 2.9 mg (6 μmole, 7%) of compound C in the title, 12.6 mg (25 μmole, 30%) of compound D in the title as well as 2.5 mg (5 μmole, 6%) of compound E in the title are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.00 (3H), 1.08 (3H), 1.16 (3H), 1.21-1.98 (9H), 1.29 (3H), 1.38 (3H), 2.07 (3H), 2.19 (1H), 2.30 (1H), 2.53 (1H), 2.81 (1H), 2.89 (1H), 3.29 (1H), 3.76 (1H), 4.37 (1H), 5.40 (1H), 6.53 (1H), 7.16 (1H), 7.29 (1H), 7.70 (1H), 8.53 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.94 (3H), 1.03 (3H), 1.11 (3H), 1.28 (3H), 1.38 (3H), 1.00-1,95 (8H), 2.14 (3H), 2.08-2.20 (1H), 2.41 (1H), 2.49 (1H), 2.83 (1H), 3.09 (1H), 3.33 (1H), 3.95 (1H), 4.06 (1H), 4.17 (1H), 5.70 (1H), 6.64 (1H), 7.12 (1H), 7.25 (1H), 7.67 (1H), 8.59 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of C: δ = 1.01 (3H), 1.04 (3H), 1.20 (3H), 1.43 (3H), 1.68 (3H), 1.12-1.93 (6H), 2.02-2.64 (5H), 2.13 (3H), 3.22 (1H), 3.38 (1H), 3.69 (1H), 4.56 (1H), 5.11 (1H), 5.18 (1H), 6.28 (1H), 7.03 (1H), 7.21 (1H), 7.37 (1H), 7.48 (1H), 8.29 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of D: δ = 1.01 (3H), 1.06 (3H), 1.18 (3H), 1.30 (3H), 1.46 (3H), 1.13-1.89 (8H), 2.14 (3H), 2.09-2.30 (2H), 2.52 (1H), 2.78 (1H), 3.17 (1H), 3.29 (1H), 3.71 (1H), 4.54 (1H), 5.37 (1H), 6.24 (1H), 6.96 (1H), 7.22 (1H), 7.37 (1H), 7.42 (1H), 8.28 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of E: δ = 0.96 (3H), 1.06 (3H), 1.10 (3H), 1.29 (3H), 1.43 (3H), 1.22-1.77 (6H), 1.78-2.18 (3H), 2.11 (3H), 2.35-2.52 (2H), 2.96 (1H), 3.31 (1H), 3.43 (1H), 3.91 (1H), 4.49 (1H), 5.42 (1H), 5.49 (1H), 7.02 (1H), 7.19 (1H), 7.33 (1H), 7.45 (1H), 8.28 (1H) ppm.

Example 22

(4S,7R,8S,9S,13(E),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione

Example 22a

(3S,6R,7S,8S,12E,15S,16E)-3,7-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-hexamethyl-15-hydroxy-17-(2-pyridyl)-5-oxo-heptadeca-12,16-dienoic acid

In analogy to Example 1i, 370 mg (444 μmole) of compound A prepared according to Example 20h are reacted, and, after work-up and purification, 309 mg (430 μmole, 97%) of the compound in the title are isolated as a colorless oil.

Example 22b

(4S,7R,8S,9S,13(E),16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1aw, 309 g (430 μmole) of the compound prepared according to Example 22a are reacted, and, after work-up and purification, 233 mg (333 μmole, 77%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.02-0.17 (12H), 0.88 (18H), 0.93 (3H), 1.09 (3H), 1.12 (3H), 1.16-1.37 (2H), 1.19 (3H), 1.45-1.64 (3H), 1.59 (3H), 1.93 (1H), 2.08-2.21 (1H), 2.18 (3H), 2.50 (1H), 2.54-2.70 (3H), 3.07 (1H), 3.90 (1H), 4.51 (1H), 5.20 (1H), 5.30 (1H), 6.58 (1H), 7.10 (1H), 7.19 (1H), 7.63 (1H), 8.60 (1H) ppm.

Example 22

(4S,7R,8S,9S,13(E),16S(E))-4,8,-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1, 228 mg (326 μmole) of the compound prepared according to Example 22b are reacted, and, after work-up and purification, 131 mg (278 μmole, 85%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.98 (3H), 1.07 (3H), 1.17 (3H), 1.31 (3H), 1.20-1.46 (3H), 1.52-1.83 (2H), 1.61 (3H), 1.98 (1H), 2.08 (3H), 2.17 (1H), 2.39 (1H), 2.41-2.66 (3H), 3.18-3.39 (2H), 3.66 (1H), 3.87 (1H), 4.38 (1H), 5.14 (1H), 5.42 (1H), 6.60 (1H), 7.13 (1H), 7.32 (1H), 7.69 (1H), 8.56 (1H) ppm.

Example 23

(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and (1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B) (1R,3S(E),7S,10R,11S,12S,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-N-oxidopyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (C) and (1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-N-oxidopyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (D)

In analogy to Example 14, 50 mg (106 μmole) of the compound prepared according to Example 20 are reacted, and, after work-up and purification, 5.3 mg (11 μmole, 10%) of compound A (or B) in the title, 4.4 mg (9 μmole, 9%) of compound B (or A) in the title, 9.6 mg (10 μmole, 9%) of compound C (or D) in the title and 11.1 mg (11 μmole, 11%) of compound D (or C) in the title are isolated.

^{1}H-NMR ($CDCl_3$) of A or B: δ = 0.94 (3H), 1.04 (3H), 1.13 (3H), 1.28 (3H), 1.39 (3H), 2.11 (3H), 1.01-2.15 (9H), 2.44 (1H), 2.58 (1H), 2.74 (1H), 2.91 (1H), 3.31 (1H), 3.73 (1H), 4.21 (1H), 4.30 (1H), 5.53 (1H), 6.53 (1H), 7.13 (1H), 7.30 (1H), 7.67 (1H), 8.57 (1H) ppm.

^{1}H-NMR ($CDCl_3$ of B or A: δ = 0.93 (3H), 1.09 (3H), 1.14 (3H), 1.28 (3H), 1.37 (3H), 1.22-2.16 (9H), 2.09 (3H), 2.46 (1H), 2.57 (1H), 2.96 (1H), 3.08 (1H), 3.26 (1H), 3.72 (1H), 3.89 (1H), 4.37 (1H), 5.47 (1H), 6.62 (1H), 7.13 (1H), 7.28 (1H), 7.68 (1H), 8.57 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of C or D: δ = 0.93 (3H), 1.06 (3H), 1.19 (3H), 1.21 (3H), 1.44 (3H), 1.15-2.01 (8H), 2.10 (3H), 2.12-2.26 (2H), 2.49 (1H), 2.89 (1H), 3.26 (1H), 3.48 (1H), 3.67 (1H), 4.63 (1H), 5.45 (1H), 5.76 (1H), 7.09 (1H), 7.21 (1H), 7.36 (1H), 7.45 (1H), 8.29 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of D or C: δ = 0.96 (3H), 1.06 (3H), 1.15 (3H), 1.24 (3H), 1.43 (3H), 1.02-2.19 (9H), 2.08 (3H), 2.23 (1H), 2.56 (1H), 2.96 (1H), 3.29 (1H), 3.68 (2H), 4.53 (1H), 5.60-5.72 (2H), 7.10 (1H), 7.21 (1H), 7.37 (1H), 7.52 (1H), 8.29 (1H) ppm.

Example 24

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

Example 24h, Variant I

(3S,6R,7S,8S,12E/Z,15S,16E)-6-Ethyl-1,3,7,15-tetrakis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-pyridyl)-heptadeca-12,16-dien-5-one

Example 24a/I

(2S)-2-Methyl-1-(tetrahydropyran-2-yloxy)-heptan-6-one

In analogy to Example 1m, 9.0 g (39.1 mmole) of the compound prepared according to Example 1v are reacted, and, after work-up and purification, 8.05 g (35.3 mmole, 90%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.93 (3H), 1.12 (1H), 1.32-1.89 (10H), 2.14 (3H), 2.42 (2H), 3.19 (1H), 3.45-3.63 (2H), 3.84 (1H), 4.56 (1H) ppm.

Example 24b/I

(2S,6E/Z,9S,10E)-9-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-11-(2-pyridyl)-1-(tetrahydropyran-2-yloxy)-2,6,10-trimethyl-undeca-6,10-diene

In analogy to Example 7ao or 20b, 1.89 g (8.28 mmole) of the compound prepared according to Example 24a/I are reacted with 10.0 g (12.4 mmole) of the compound prepared according to Example 20a using n-butyllithium as base, and, after work-up and purification, 1.98 g (3.2 mmole, 38%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.81-0.92 (3H), 1.08 (9H), 1.18-1.92 (16H), 2.02 (3H), 2.19-2.42 (2H), 3.02-3.62 (3H), 3.83 (1H), 4.20 (1H), 4.55 (1H), 5.00 (1H), 6.24 (1H), 6.98-7.10 (2H), 7.22-7.46 (6H), 7.57 (1H), 7.62-7.75 (4H), 8.58 (1H) ppm.

Example 24c/I

(2S,6E/Z,9S,10E)-11-(2-Pyridyl)-1-(tetrahydropyran-2-yloxy)-2,6,10-trimethyl-undeca-6,10-dien-9-ol

In analogy to Example 1i, 1.98 g (3.2 mmole) of the compound prepared according to Example 24b/I are reacted, and, after work-up and purification, 1.16 g (3.0 mmole, 94%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.87-1.00 (3H), 1.12 (1H), 1.32-1.95 (11H), 1.67 + 1.73 (3H), 1.98-2.18 (2H), 2.10 (3H), 2.40 (2H), 3.08-3.28 (1H), 3.42-3.65 (2H), 3.84 (1H), 4.19 (1H), 4.55 (1H), 5.19 (1H), 6.59 (1H), 7.10 (1H), 7.24 (1H), 7.63 (1H), 8.60 (1H) ppm.

Example 24d/I

(2S,6E/Z,9S,10E)-9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-11-(2-pyridyl)-1-(tetrahydro-pyran-2-yloxy)-2,6,10-trimethyl-undeca-6,10-diene

In analogy to Example 1n, 1.15 g (2.97 mmole) of the compound prepared according to Example 24c/I are reacted, and, after work-up and purification, 1.43 g (2.85 mmole, 96%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.03 (3H), 0.08 (3H), 0.81-0.98 (12H), 1.11 (1H), 1.28-2.10 (12H), 1.60 + 1.69 (3H), 2.06 (3H), 2.28 (2H), 3.07-3.27 (1H), 3.42-3.63 (2H), 3.85 (1H), 4.12 (1H), 4.56 (1H), 5.18 (1H), 6.48 (1H), 7.08 (1H), 7.22 (1H), 7.62 (1H), 8.60 (1H) ppm.

Example 24e/I

(2S,6E/Z,9S,10E)-9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-11-(2-pyridyl)-2,6,10-tri-methyl-undeca-6,10-dien-1-ol

In analogy to Example 1f, 1.43 g (2.85 mmole) of the compound prepared according to Example 24d/I is reacted at 23°C using p-toluenesulfonic acid monohydrate, and, after work-up and purification, 1.11 g (2.66 mmole, 93%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.03 (3H), 0.08 (3H), 0.82-0.96 (12H), 0.97-1.71 (6H), 1.59 + 1.69 (3H), 1.90-2.14 (2H), 2.04 (3H), 2.30 (2H), 3.35-3.56 (2H), 4.13 (1H), 5.13 + 5.21 (1H), 6.48 (1H), 7.10 (1H), 7.25 (1H), 7.63 (1H), 8.58 (1H) ppm.

Example 24f/I

(2S,6E/Z,9S,10E)-9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-11-(2-pyridyl)-2,6,10-tri-methyl-undeca-6,10-dienal

In analogy to Example 1k, 1.01 g (242 mmole) of the compound prepared according to Example 24e/I are reacted, and, after work-up and purification, 921 mg (2.22 mmole, 92%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.03 (3H), 0.08 (3H), 0.92 (9H), 1.05 + 1.09 (3H), 1.22-1.75 (4H), 1.60 + 1.68 (3H), 1.95-2.11 (2H), 2.07 (3H), 2.23-2.38 (3H), 4.12 (1H), 5.19 (1H), 6.48 (1H), 7.08 (1H), 7.22 (1H), 7.63 (1H), 8.60 (1H), 9.57 + 9.61 (1H) ppm.

Example 24g/I

(3S,6R,7S,8S,12E/Z,15S,16E)-6-Ethyl-7-hydroxy-1,3,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-pyridyl)-heptadeca-12,16-dien-5-one(A) and (3S,6S,7R,8S,12E/Z,15S,16E)-6-ethyl-7-hydroxy-1,3,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-pyridyl)-heptadeca-12,16-dien-5-one(B)

In analogy to Example 1ak, 1.0 g (2.41 mmole) of the compound prepared according to Example 24f/I is reacted with 1.16 g (2.78 mmole) of the compound prepared according to Example 1m, and, after work-up and purification, 9.72 mg (1.17 mmole, 48%) of compound A in the title, as well as 178 mg (0.21 mmole, 9%) of compound B in the title are isolated, each as a colorless oil.

^{1}H-NMR ($CDCl_3$ of A: δ = 0.00-0.14 (18H), 0.80-0.95 (33H), 1.00-1.81 (9H), 1.11 (3H), 1.17 (3H), 1.60 + 1.68 (3H), 1.90-2.11 (2H), 2.04 (3H), 2.29 (2H), 3.03 (1H), 3.18 (1H), 3.32 (1H), 3.54-3.77 (2H), 3.99 (1H), 4.12 (1H), 5.18 (1H), 6.48 (1H), 7.09 (1H), 7.23 (1H), 7.62 (1H), 8.69 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = -0.02-0.14 (18H), 0.83-1.01 (33H), 1.02-1.80 (9H), 1.10 (3H), 1.16 (3H), 1.62 + 1.70 (3H), 1.92-2.10 (2H), 2.06 (3H), 2.30 (2H), 3.02 (1H), 3.15 (1H), 3.42 (1H), 3.53-3.74 (2H), 4.02 (1H), 4.12 (1H), 5.19 (1H), 6.49 (1H), 7.09 (1H), 7.23 (1H), 7.63 (1H), 8.60 (1H) ppm.

Example 24h/I

(3S,6R,7S,8S,12E/Z,15S,16E)-6-Ethyl-1,3,7,15-tetrakis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-pyridyl)-heptadeca-12,16-dien-5-one

In analogy to Example 1aq, 972 mg (1.17 mmole) of compound A prepared according to Example 24g/I are reacted, and, after work-up and purification, 1.02 g (1.08 mmole, 92%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.00-0.12 (24H), 0.78-0.97 (42H), 1.00-1.80 (9H), 1.03 (3H), 0.21 (3H), 1.60 + 1.68 (3H), 1.90-2.10 (2H), 2.05 (3H), 2.28 (2H), 3.02 (1H), 3.52-3.73 (2H), 3.82 (1H), 3.91 (1H), 4.11 (1H), 5.19 (1H), 6.49 (1H), 7.08 (1H), 7.22 (1H), 7.61 (1H), 8.60 (1H) ppm.

Example 24h, Variant II

(3S,6R,7S,8S,12E/Z,15S,16E)-6-Ethyl-1,3,7,15-tetrakis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-pyridyl)-heptadeca-12,16-dien-5-one

Example 24a/II

(4S(4R,5S,6S,10E/Z,13S,14E))-4-(13-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-ethyl-15-(2-pyridyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-2,6,10,14-tetramethyl-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane

In analogy to Example 1ao and 20b, respectively, [724 mg (1.59 mmole) of the compound prepared according to Example 1an are reacted with 1.93 g (2.40 mmole) of the compound prepared according to Example 20a, using n-butyllithium as base, and, after work-up and purification, 478 mg (0.56 mmole, 35%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.72-1.96 (48H), 2.01 (3H), 2.16-2.41 (2H), 3.03 + 3.13 (1H), 3.41 (1H), 3.59-4.04 (3H), 4.12-4.32 (2H), 4.43 + 4.52 (1H), 5.01 (1H), 6.23 (1H), 6.97-7.10 (2H), 7.21-7.46 (6H), 7.58 (1H), 7.62-7.74 (4H), 8.57 (1H) ppm.

Example 24b/II

(4S(4R,5S,6S,10E/Z,13S,14E))-4-(4-Ethyl-13-hydroxy-15-(2-pyridyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-2,6,10,14-tetramethyl-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]-dioxane

In analogy to Example 1i, 660 mg (0.77 mmole) of the compound prepared according to Example 24a/II are reacted, and, after work-up and purification, 475 mg (0.77 mmole, 100%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.72-2.12 (39H), 2.09 (3H), 2.39 (2H), 3.07 + 3.17 (1H), 3.42 (1H), 3.62-4.32 (6H), 4.43 + 4.54 (1H), 5.20 (1H), 6.61 (1H), 7.10 (1H), 7.25 (1H), 7.63 (1H), 8.60 (1H) ppm.

Example 24c/II

(3S,6R,7S,8S,12E/Z,15S,16E)-6-Ethyl-1,3,7,15-tetrahydroxy-4,4,8,12,16-pentamethyl-17-(2-pyridyl)-heptadeca-12,16-dien-5-one

In analogy to Example 1f, 472 mg (0.77 mmole) of the compound prepared according to Example 24b/II is reacted at 23°C using p-toluenesulfonic acid monohydrate, and, after

work-up and purification, 348 mg (0.71 mmole, 92%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.75-0.92 (6H), 1.07 (3H), 1.11-2.47 (13H), 1.26 (3H), 1.63 (3H), 1.72 (3H), 2.04 + 2.05 (3H), 2.96 (1H), 3.18 (1H), 3.41 + 3.48 (1H), 3.86 (2H), 4.04-4.23 (2H), 5.18 + 5.23 (1H), 6.57 (1H), 7.12 (1H), 7.29 (1H), 7.67 (1H), 8.59 (1H) ppm.

Example 24h/II

(3S,6R,7S,8S,12E/Z,15S,16E)-6-Ethyl-1,3,7,15-tetrakis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-pyridyl)-heptadeca-12,16-dien-5-one

In analogy to Example 1aq, 343 mg (0.70 mmole) of the compound prepared according to Example 24c/II are reacted, and, after work-up and purification, 497 mg (0.52 mmole, 75%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): superimosable with that described under example 24h/I

Example 24i

(3S,6R,7S,8S,12E/Z,15S,16E)-6-Ethyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-1-hydroxy-17-(2-pyridyl)-heptadeca-12,16-dien-5-one

In analogy to Example 1ar, 1.71 g (1.81 mmole) of the compound prepared according to Example 24h/I or Example 24h/II are reacted, and, after work-up and purification, 1.38 g (1.66 mmole, 97%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.00-0.15 (18H), 0.80-0.98 (33H), 1.02-2.10 (11H), 1.09 (3H), 1.21 (3H), 1.59 + 1.68 (3H), 2.05 (3H), 2.29 (2H), 3.01 (1H), 3.69 (2H), 3.84 (1H); 4.02-4.19 (3H), 5.18 (1H), 6.48 (1H), 7.09 (1H), 7.22 (1H), 7.62 (1H), 8.59 (1H) ppm.

Example 24k

(3S,6R,7S,8S,12E/Z,15S,16E)-6-Ethyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-pyridyl)-5-oxo-heptadeca-12,16-dienal

In analogy to Example 1k, 1.38 g (1.66 mmole) of the compound prepared according to Example 24i are reacted, and, after work-up and purification, 1.34 g (1.61 mmole, 97%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.01-0.13 (18H), 0.78-0.97 (35H), 1.09 (3H), 1.13-1.79 (5H), 1.21 (3H), 1.60 + 1.68 (3H), 1.91-2.10 (2H), 2.05 (3H), 2.28 (2H), 2.40 (1H), 2.57 (1H), 3.02

(1H), 3.82 (1H), 4.12 (1H), 4.48 (1H), 5.18 (1H), 6.48 (1H), 7.08 (1H), 7.22 (1H), 7.62 (1H), 8.60 (1H), 9.79 (1H) ppm.

Example 24l

(3S,6R,7S,8S,12E,15S,16E)-6-Ethyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-pyridyl)-5-oxo-heptadeca-12,16-dienoic acid (A) and (3S,6R,7S,8S,12Z,15S,16E)-6-ethyl-3,7,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,8,12,16-pentamethyl-17-(2-pyridyl)-5-oxo-heptadeca-12,16-dienoic acid (B)

In analogy to Example 1at, 1.34 g (1.61 mmole) of the compound prepared according to Example 24k are reacted, and, after work-up and purification, 433 mg (0.51 mmole, 32%) of compound A in the title, as well as 662 mg (0.78 mmole, 49%) of compound B in the title are isolated, each as a colorless oil.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.00-0.16 (18H), 0.78-0.93 (35H), 0.98-1.71 (6H), 1.12 (3H), 1.21 (3H), 1.56 (3H), 1.80-2.07 (2H), 1.93 (3H), 2.23-2.41 (3H), 2.67 (1H), 3.05 (1H), 3.86 (1H), 4.12 (1H), 4.33 (1H), 5.11 (1H), 6.48 (1H), 7.24 (1H), 7.33 (1H), 7.69 (1H), 8.61 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = -0.01-0.17 (18H), 0.81-0.96 (35H), 1.00-1.78 (6H), 1.15 (3H), 1.21 (3H), 1.70 (3H), 1.89 (1H), 1.96 (3H), 2.11-2.42 (4H), 2.59 (1H), 3.00 (1H), 3.82 (1H), 4.17 (1H), 4.41 (1H), 5.24 (1H), 6.63 (1H), 7.19 (1H), 7.33 (1H), 7.71 (1H), 8.64 (1H) ppm.

Example 24m

(3S,6R,7S,8S,12Z,15S,16E)-3,7-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-6-ethyl-4,4,8,12,16-pentamethyl-15-hydroxy-17-(2-pyridyl)-5-oxo-heptadeca-12,16-dienoic acid

In analogy to Example 1i, 662 mg (0.78 mmole) of the compound B prepared according to Example 24l are reacted at 23°C, and, after work-up, 680 mg of the compound in the title are isolated as crude product, which is reacted further without purification.

Example 24n

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-ethyl-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1aw, 680 mg (maximum 0.78 mmole) of the compound prepared according to Example 24m are reacted, and, after work-up and purification, 287 mg (402 μmole, 52%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = -0.11 (3H), 0.03-0.15 (9H), 0.72 (3H), 0.80-1.78 (23H), 0.83 (3H), 0.92 (3H), 0.98 (3H), 1.11 (3H), 1.18 (3H), 1.68 (3H), 1.85 (1H), 2.09 (1H), 2.12 (3H), 2.46 (1H), 2.55-2.82 (3H), 3.05 (1H), 4.01 (1H), 4.03 (1H), 4.99 (1H), 5.16 (1H), 6.54 (1H), 7.08 (1H), 7.23 (1H), 7.61 (1H), 8.58 (1H) ppm.

Example 24

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1, 282 mg (395 μmole) of the compound prepared according to Example 24n are reacted, and, after work-up and purification, 115 mg (237 μmole, 60%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.89 (3H), 1.04 (3H), 1.09 (3H), 1.22-2.11 (8H), 1.36 (3H), 1.70 (3H), 2.07 (3H), 2.20-2.39 (3H), 2.49 (1H), 2.65 (1H), 2.69 (1H), 3.23 (1H), 3.70 (1H), 4.35 (1H), 4.59 (1H), 5.12 (1H), 5.19 (1H), 6.61 (1H), 7.13 (1H), 7.29 (1H), 7.69 (1H), 8.53 (1H) ppm.

Example 25

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and (1R,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B) and (4S,7R,8S,9S,13(Z),16S(E))-4,8-dihydroxy-9-ethyl-16-(1-methyl-2-(2-N-oxypyridyl)ethenyl)-1-oxa-5,5,7,13-tetramethyl-cyclohexadec-13-ene-2,6-dione (C) and (1S,3S(E),7S,10R,11S,12S,16R)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-N-oxypyridyl)-ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (D) and (1R,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-N-oxypyridyl)-ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (E)

In analogy to Example 14, 50 mg (103 μmole) of the compound prepared according to Example 24 are reacted, and, after work-up and purification, 15.3 mg (30 μmole, 30%) of the compound A in the title, 2 mg (4 μmole, 4%) of compound B in the title, 2 mg (4

μmole, 4%) of compound C in the title, 21 mg (42 μmole, 41%) of compound D in the title and 3.3 mg (7 μmole, 6%) of compound E in the title are isolated, each as a colorless solid.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.87 (3H), 0.99 (3H), 1.06 (3H), 1.21-2.03 (10H), 1.30 (3H), 1.39 (3H), 2.03 (3H), 2.15 (1H), 2.37 (1H), 2.56 (1H), 2.81 (1H), 2.83 (1H), 3.32 (1H), 3.66 (1H), 4.36 (1H), 5.24 (1H), 5.45 (1H), 6.61 (1H), 7.16 (1H), 7.29 (1H), 7.70 (1H), 8.53 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.85 (3H), 0.95 (3H), 1.04 (3H), 1.20-1.93 (10H), 1.30 (3H), 1.38 (3H), 2.08 (1H), 2.11 (3H), 2.42-2.61 (2H), 2.95 (1H), 2.98 (1H), 3.22 (1H), 3.63 (1H), 3.93 (1H), 4.33 (1H), 5.59 (1H), 6.66 (1H), 7.13 (1H), 7.28 (1H), 7.67 (1H), 8.58 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of C: δ = 0.80-1.92 (8H), 0.92 (3H), 1.03 (3H), 1.08 (3H), 1.44 (3H), 1.70 (3H), 2.08-2.64 (5H), 2.12 (3H), 2.82 (1H), 3.29 (1H), 3.67 (1H), 4.53 (1H), 5.09 (1H), 5.17 (1H), 6.19 (1H), 6.99 (1H), 7.19 (1H), 7.35 (1H), 7.44 (1H), 8.29 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of D: δ = 0.87 (3H), 1.00 (3H), 1.04 (3H), 1.09-2.03 (10H), 1.29 (3H), 1.42 (3H), 2.10 (3H), 2.18-2.32 (2H), 2.53 (1H), 2.67-2.82 (2H), 3.31 (1H), 3.62 (1H), 4.52 (1H), 5.41 (1H), 6.16 (1H), 6.93 (1H), 7.21 (1H), 7.37 (1H), 7.42 (1H), 8,28 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of E: δ = 0.83 (3H), 0.94 (3H), 1.08 (3H), 1.20-2.08 (11H), 1.29 (3H), 1.45 (3H), 2.12 (3H), 2.39-2.56 (2H), 2.87 (1H), 3.24 (1H), 3.29 (1H), 3.87 (1H), 4.52 (1H), 5.41 (1H), 5.56 (1H), 7.03 (1H), 7.19 (1H), 7.34 (1H), 7.46 (1H), 8.29 (1H) ppm.

Example 26

(4S,7R,8S,9S,13(E),16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

Example 26a

(3S,6R,7S,8S,12E,15S,16E)-3,7-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-6-ethyl-4,4,8,12,16-pentamethyl-15-hydroxy-17-(2-pyridyl)-5-oxo-heptadeca-12,16-dienoicacid

In analogy to Example 1i, 433 mg (0.51 mmole) of compound A prepared according to Example 24l is reacted, and, after work-up, 477 mg of the compound in the title are isolated as crude product, which is reacted further without purification.

Example 26b

(4S,7R,8S,9S,13(E),16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-7-ethyl-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1aw, 447 mg (511 μmole) of the compound prepared according to Example 26a are reacted, and, after work-up and purification, 264 mg (370 μmole, 72%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.06-0.15 (12H), 0.85 (3H), 0.89 (9H), 0.91 (9H), 0.94 (3H), 1.08-1.92 (11H), 1.12 (3H), 1.21 (3H), 2.10-2.23 (1H), 2.16 (3H), 2.40 (1H), 2.46-2.68 (3H), 2.98 (1H), 3.95 (1H), 4.41 (1H), 5.23 (1H), 5.30 (1H), 6.57 (1H), 7.10 (1H), 7.21 (1H), 7.63 (1H), 8.60 (1H) ppm.

Example 26

(4S,7R,8S,9S,13(E),16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

In analogy to Example 1, 260 mg (364 μmole) of the compound prepared according to Example 26b are reacted, and, after work-up and purification, 121 mg (249 μmole, 68%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.83 (3H), 0.90 (1H), 0.98 (3H), 1.01 (3H), 1.31 (3H), 1.37-2.00 (7H), 1.61 (3H), 2.08 (3H), 2.18 (1H), 2.37-2.52 (3H), 2.60 (1H), 3.35 (1H), 3.70 (1H), 3.83-4.32 (2H), 4.45 (1H), 5.08 (1H), 5.39 (1H), 6.58 (1H), 7.13 (1H), 7.35 (1H), 7.68 (1H), 8.53 (1H) ppm.

Example 27

(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and (1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B) (1R,3S(E),7S,10R,11S,12S,16R)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-N-oxidopyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (C) and (1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-N-oxidopyridyl)ethenyl)-8,8,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (D)

In analogy to Example 14, 59 mg (121 μmole) of the compound prepared according to Example 26 are reacted, and, after work-up and purification, 5 mg (10 μmole, 8%) of

compound A or B in the title, 2 mg (4 μmole, 3%) of compound B or A in the title, 14 mg (27 μmole, 22%) of compound C or D in the title and 6.9 mg (13 μmole, 11%) of compound D or C in the title are isolated, each as a colorless solid.

^{1}H-NMR ($CDCl_3$) of A or B: δ = 0.83 (3H), 0.92 (3H), 1.02 (3H), 1.09-2.19 (12H), 1.27 (3H), 1.37 (3H), 2.11 (3H), 2.43-2.61 (2H), 2.88 (1H), 3.31 (1H), 3.78 (1H), 4.26 (1H), 4.33 (1H), 5.48 (1H), 6.64 (1H), 7.12 (1H), 7.30 (1H), 7.67 (1H), 8.57 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B or A: δ = 0.86 (3H), 0.93 (3H), 1.09 (3H), 1.19-2.19 (11H), 1.27 (3H), 1.38 (3H), 2.10 (3H), 2.50-2.63 (2H), 2.87 (1H), 2.98 (1H), 3.28 (1H), 3.71 (1H), 3.88 (1H), 4.31 (1H), 5.48 (1H), 6.62 (1H), 7.13 (1H), 7.28 (1H), 7.67 (1H), 8.58 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of C or D: δ = 0.84 (3H), 0.91 (3H), 1.06 (3H), 1.11-2.08 (10H), 1.26 (3H), 1.38 (3H), 2.02 (3H), 2.19 (1H), 2.37 (1H), 2.53 (1H), 2.92 (1H), 3.34 (1H), 3.56-3.72 (2H), 4.53 (1H), 5.05 (1H), 5.60 (1H), 6.99 (1H), 7.21 (1H), 7.33 (1H), 7.45 (1H), 8.28 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of D or C: δ = 0.84 (3H), 0.89 (3H), 1.07 (3H), 1.15-2.23 (11H), 1.22 (3H), 1.43 (3H), 2.09 (3H), 2.36 (1H), 2.53 (1H), 2.97 (1H), 3.02 (1H), 3.32 (1H), 3.58 (1H), 4.58 (1H), 5.44 (1H), 5.58 (1H), 7.06 (1H), 7.21 (1H), 7.36 (1H), 7.44 (1H), 8.29 (1H) ppm.

Example 28

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7,9,13-trimethyl-5,5-trimethylene-cyclohexadec-13-ene-2,6-dione

Example 28a

1,1-Cyclobutane dimethanol

To a solution of 20 g (99.9 mmole) of 1,1-cyclobutane dicarboxylic acid diethyl ester in 200 mL of absolute tetrahydrofuran, at 0°C, 170 mL of a 1.2 molar solution of diisobutyl-aluminum hydride are added dropwise. The mixture is stirred for one hour at 0°C and then 30 mL of water are added. The mixture is filtered through Celite. The filtrate is dried with sodium sulfate and evaporated in vacuum. The obtained crude product (9.9 g, 85.2 mmole, 85) is used in the next step without purification.

Example 28b

1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutanemethanol

To a suspension of 3.4 g of sodium hydride (60% in oil) in 35 mL of absolute tetrahydrofuran, a solution of 9.9 g (85 mmole) of the compound prepared according to Example 28a in 100 mL of absolute tetrahydrofuran are added at 0°C. The mixture is stirred for 30 minutes and then a solution of 12.8 g of *tert.*-butyldimethylsilyl chloride in 50 mL of tetrahydrofuran is added. The mixture is stirred for one hour at 25°C and then the reaction mixture is poured into saturated aqueous sodium hydrogen carbonate solution. It is extracted with ethyl acetate. The organic phase is washed with saturated sodium chloride solution and dried over sodium sulfate. After removal of the solvent in vacuum, the obtained crude product is purified by column chromatography on silica gel with a mixture of hexane/ethyl acetate. Thus, 13.5 g (58.6 mmole, 69%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.04 (6H), 0.90 (9H), 1.70-2.00 (6H), 3.70 (4H) ppm.

Example 28c

1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutanecarbaldehyde

Analogously to Example 1k, starting from 13.5 g (58.6 mmole) of the compound described under 28b, after purification, 7.7 g (33.7 mmole, 58%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 9.70 s (1H), 3.83 s (2H), 2.20-2.30 m (2H), 1.85-2.00 m (4H), 0.90 s (9H), 0.03 s (6H) ppm.

Example 28d

[1*R*-[1α(*R),2β]]-2-Phenylcyclohexyl-3-[1-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]-cyclobutyl]-3-hydroxypropanoate (A) and**

[1*R*-[1α(*S),2β]]-2-Phenylcyclohexyl-3-[1-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]-cyclobutyl]-3-hydroxypropanoate (B)**

Starting from 7.2 mL of diisopropylamine and butyllithium (32 mL of a 1.6 molar solution in hexane), lithium diisopropylamide is prepared in absolute tetrahydrofuran. Then, at -78°C, a solution of 11.2 g of (1*R*-*trans*)-2-phenylcyclohexyl acetate in 100 mL of absolute tetrahydrofuran is added and stirring is continued for 30 minutes at this temperature. Then a solution of 7.7 g (33.7 mmole) of the compound prepared according to Example 28c in 50 mL of

tetrahydrofuran is added. The reaction mixture is stirred for 1.5 hours at -78°C and then is poured into saturated aqueous ammonium chloride solution. It is extracted with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After chromatography of the crude product on a silica gel column with a mixture of hexane/ethyl acetate, 6.34 g (14.2 mmole, 42%) of compound A in the title and 4.22 g (9.4 mmole, 28%) of compound B in the title are obtained.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.04 (6H), 0.98 (9H), 2.69 (1H), 3.08 (1H), 3.60 (1H), 3.67 (1H), 3.78-3.84 (1H), 4.97 (1H), 7.15-7.30 (5H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.03 (6H), 0.90 (9H), 2.68 (1H), 2.80 (1H), 3.56 (2H), 3.68-3.72 (1H), 4.99 (1H), 7.18-7.30 m (5H) ppm.

Example 28e

(*S*)-1-[1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutyl]-1,3-propanediol

To a solution of 1 g (2.24 mmole) of compound A prepared according to Example 28d in 10 mL of absolute toluene, 4 mL of a 1.2 molar solution of diisobutylaluminum hydride in toluene are added dropwise at 0°C. The mixture is stirred for 1.5 hours at 0°C and then 5 mL of water are added, followed by filtration through Celite. The filtrate is dried over sodium sulfate and evaporated in vacuum. After chromatography of the crude product on a silica gel column with a mixture of hexane/ethyl acetate, 370 mg (1.35 mmole, 60%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.05 (6H), 0.90 (9H), 1.55-1.60 (2H), 1.80 (2H), 1.90 (3H), 2.10 (1H), 3.75 (1H), 3.85-3.95 (4H) ppm.

Example 28f

(*S*)-2,2-Dimethyl-4-[1-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobutyl]-1,3-dioxane

Analogously to Example 1h, starting from 370 mg (1.35 mmole) of the compound described under 28e, after purification, 338 mg (1.07 mmole, 79%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.03 (6H), 0.88 (9H), 1.38 (3H), 1.42 (3H), 1.50-1.80 (4H), 2.00 (1H), 3.52 (1H), 3.62 (1H), 3.85-4.00 (3H) ppm.

Example 28g

(*S*)-1-(2,2-Dimethyl-1,3-dioxan-4-yl)cyclobutanemethanol

1.27 g (4.04 mmole) of the compound prepared according to Example 28f are reacted analogously to 1i with 6 mL of a 1 molar solution of tetrabutylammonium chloride in tetrahydrofuran. After column chromatography, 794 mg (98%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 1.38 (3H), 1.46 (3H), 1.55-1.67 (2H), 1.75-2.05 (6H), 2.97 (1H), 3.62 (1H), 3.84-4.10 (4H) ppm.

Example 28h

(*S*)-1-(2,2-Dimethyl-1,3-dioxan-4-yl)cyclobutanecarbaldehyde

In analogy to Example 1k, 794 mg (3.97 mmole), 28 g [sic] are reacted and 786 mg (100%) of the compound in the title are isolated as a crude product, which is used in the next step without purification.

Example 28i

(*S*)-1-(2,2-Dimethyl-1,3-dioxan-4-yl)-α-ethylcyclobutanemethanol

In analogy to Example 1l, 786 mg (3.97 mmole) of the compound described under 28h are reacted with a 2 molar solution of ethylmagnesium chloride in tetrahydrofuran. After purification, 835 mg (95%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 1.05 (3H), 1.38 (3H), 1.49 (3H), 1.60-2.10 (8H), 2.60 (1H), 2.83 (1H), 3.50 (1H), 3.85-4.15 (3H) ppm.

Example 28k

(*S*)-1-[1-(2,2-Dimethyl-1,3-dioxan-4-yl)cyclobutyl]propan-1-one

In analogy to Example 1m, starting from 835 mg (3.67 mmole) of the compound described under 28i, 689 mg (83%) of the compound in the title are obtained after purification.

^{1}H-NMR ($CDCl_3$): δ = 1.03 (3H), 1.35 (1H), 1.36 (3H), 1.45 (3H), 1.55 (1H), 1.65-1.90 (2H), 2.02 (1H), 2.14-2.30 (2H), 2.33 (1H), 2.45-2.60 (2H), 3.80-4.00 (2H), 4.10 (1H) ppm.

Example 28l

(S)-1-[1-(1,3-Dihydroxypropyl)cyclobutyl]propan-1-one

680 mg (3 mmole) of the compound described under 28k are dissolved in 30 mL of tetrahydrofuran. Then 1 mL of water and 30 mg of p-toluonesulfonic acid are added, followed by stirring for 30 minutes at 50°C. After work-up and purification, 471 mg (84%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 1.05 (3H), 1.10 (1H), 1.53 (1H), 1.65 (1H), 1.80-2.00 (3H), 2.15 (1H), 2.40-2.70 (3H), 3.35 (1H), 3.55 (1H), 3.88 (1H), 4.10 (1H) ppm.

Example 28m

(S)-1-(1,3-Bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]cyclobutyl)propan-1-one

Analogously to Example 1aq, from 470 mg (2.54 mmole) of the compound described under 28l, after purification, 709 mg (68%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.02 (6H), 0.15 (3H), 0.17 (3H), 0.90 (9H), 0.94 (9H), 1.05 (3H), 1.30-1.53 (2H), 1.70-1.85 (2H), 1.98 (1H), 2,23 (3H), 2.45-2.53 (2H), 3.54 (2H), 4.11 (1H) ppm.

Example 28n

(2S,6E/Z,9S,10E)-9-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-11-(2-methylthiazol-4-yl)-1-(tetrahydropyran-2-yloxy)-2,6,10-trimethyl-undeca-6,10-diene

Analogously to Example 24b/I, from 2.24 g (9.84 mmole) of the compound described under 24a/I and 12.2 g (14.81 mmole) of the compound described under 1ai, using butyllithium as base, 3.01 g (47%) of the compound in the title are obtained after purification.

^{1}H-NMR ($CDCl_3$): δ = 0.86 (3H), 1.04 (9H), 1.55 + 1.60 (3H), 1.30 (2H), 1.99 (3H), 2.25 (2H), 2.70 (3H), 1.10-3.20 (1H), 3.45-3.60 (2H), 3.86 (1H), 4.14 (1H), 4.54 (1H), 4.97 (1H), 6.22 (1H), 6.78 (1H), 7.30-7.50 (6H), 7.60-7.70 (4H) ppm.

Example 28o

(2S,6E/Z,9S,10E)-11-(2-Methylthiazolyl-4-yl)-1-(tetrahydropyran-2-yloxy)-2,6,10-trimethyl-undeca-6,10-dien-9-ol

Analogously to Example 1i, from 7.65 g (11.84 mmole) of the compound described under 28n, 4.53 g (94%) of the compound in the title are obtained after purification.

^{1}H-NMR ($CDCl_3$): δ = 0.91 (3H), 1.10 (1H), 1.65 + 1.71 (3H), 2.04 (3H), 2.39 (2H), 2.70 (3H), 3.12 + 3.21 (1H), 3.50 + 3.58 (2H), 3.85 (1H), 4.14 (1H), 4.55 (1H), 5.15 (1H), 6.56 (1H), 6.93 (1H) ppm.

Example 28p

(2S,6E/Z,9S,10E)-9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-11-(2-methylthiazol-4-yl)-1-(tetrahydropyran-2-yloxy)-2,6,10-trimethyl-undeca-6,10-diene

Analogously to Example 1ad, from 4.53 g of the compound described under 28o, 5.68 g (98%) of the compound in the title are obtained after purification.

^{1}H-NMR ($CDCl_3$): δ = 0.00 (3H), 0.03 (3H), 0.90 (12H), 1.56 + 1.64 (3H), 1.99 (3H), 2.21 (2H), 3.10 + 3.20 (1H), 3.45 -3.60 (2H), 3.85 (1H), 4.10 (1H), 4.57 (1H), 5.12 (1H), 6.45 (1H), 6.90 (1H) ppm.

Example 28q

(2S,6E/Z,9S,10E)-9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-11-(2-methylthiazol-4-l[sic])-2,6,10-trimethyl-undeca-6,10-dien-1-ol

Analogously to Example 1f (2 hours of reaction time at 50°C), from 5.68 g (10.88 mmole) of the compound described under 28p, 4.02 g (84%) of the compound in the title are obtained after purification.

^{1}H-NMR ($CDCl_3$): δ = 0.00 (3H), 0.05 (3H), 0.90 (12H), 1.60 + 1.65 (3H), 2.00 (3H), 2.23 (2H), 2.71 (3H), 3.38-3.55 (2H), 4.10 (1H), 5.09 + 5.14 (1H), 6.45 + 6.48 (1H), 6.91 + 6.93 (1H) ppm.

Example 28r

(2S,6E/Z,9S,10E)-9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-11-(2-methylthiazol-4-yl)-2,6,10-trimethyl-undeca-6,10-dien-1-al

Analogously to Example 1k, from 667 mg (1.5 mmole) of the compound described under 28q, after filtration through silica gel, 648 mg (98%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.01 (3H), 0.06 (3H), 0.90 (9H), 1.06 + 1.09 (3H), 1.58 + 1.66 (3H), 2.00 (3H), 4.10 (1H), 5.13 (1H), 6.46 (1H), 6.91 + 6.93 (1H) ppm.

Example 28s

(3S,6R,7S,8S,12Z,15S,16E)-7-Hydroxy-1,3,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-6,8,12,16-tetramethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-heptadeca-12,16-dien-5-one (A) and

(3S,6R,7S,8S,12E,15S,16E)-7-hydroxy-1,3,15-tris-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-6,8,12,16-tetramethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-heptadeca-12,16-dien-5-one (B)

Analogously to Example 1ak, from 709 mg (1.71 mmole) of the compound described under 28m and 667 mg (1.52 mmole) of the compound described under 28r, after purification, 352 mg (27%) of compound A in the title and 227 mg (17%) of compound B in the title are obtained.

^{1}H-NMR ($CDCl_3$) of compound A: δ = 0.00 (3H), 0.04 (9H), 0.14 (3H), 0.16 (3H), 0.80 (3H), 0.88 (18H), 0.91 (9H), 1.03 (3H), 1.68 (3H), 2.00 (3H), 2.20-2.40 (3H), 2.72 (3H), 3.25 (1H), 3.44 (1H), 3.58 (3H), 4.10 (2H), 5.13 (1H), 6.42 (1H), 6.93 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of compound B: δ = 0.00 (3H), 0.04 (6H), 0.08 (3H), 0.15 (3H), 0.18 (3H), 0.80 (3H), 0.89 (18H), 0.92 (9H), 1.05 (3H), 1.60 (3H), 2.00 (3H), 2.20-2.40 (3H), 2.70 (3H), 3.25 (1H), 3.45 (1H), 3.60 (3H), 4.10 (2H), 5.15 (1H), 6,45 (1H), 6.91 (1H) ppm.

Example 28t

(3S,6R,7S,8S,12Z,15S,16E)-1,3,7,15-Tetrakis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-6,8,12,16-tetramethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-heptadeca-12,16-dien-5-one

Analogously to Example 1aq, from 352 mg (0.41 mmole) of compound A described under 28s, 381 mg (95%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.00 (3H), 0.02 (6H), 0.04 (3H), 0.07 (3H), 0.09 (3H), 0.13 (3H), 0.16 (3H), 0.90 (18H), 0.94 (18H), 0.95 (3H), 1.09 (3H), 1.68 (3H), 2.20-2.40 (3H) [sic] (83H), 2.71 (3H), 3.10 (1H), 3.58 (2H), 3.78 (1H), 4.10 (2H), 5.13 (1H), 6.47 (1H), 6.90 (1H) ppm.

Example 28u

(3S,6R,7S,8S,12Z,15S,16E)-3,7,15-tris-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-1-hydroxy-6,8,12,16-tetramethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-heptadeca-12,16-dien-5-one

Analogously to Example 1ar, from 381 mg (0.39 mmole) of the compound described under 28t, 289 mg (86%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.01 (3H), 0.05 (3H), 0.08 (3H), 0.11 (3H), 0.16 (3H), 0.18 (3H), 0.90-1.00 (30H), 1.10 (3H), 1.67 (3H), 1.99 (3H), 2.20-2.40 (3H), 2.71 (3H), 3.14 (1H), 3.63 (2H), 3.82 (1H), 4.09 (2H), 5.12 (1H), 6.46 (1H), 6.92 (1H) ppm.

Example 28v

(3S,6R,7S,8S,12Z,15S,16E)-3,7,15-tris-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-6,8,12,16-tetramethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-5-oxo-heptadeca-12,16-dien-1-al

Analogously to Example 1k, from 285 mg (0.34 mmole) of the compound described under 28u, after filtration through silica gel, 284 mg (100%) of the compound in the title are obtained.

Example 28w

(3S,6R,7S,8S,12Z,15S,16E)-3,7,15-tris-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-6,8,12,16-tetramethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-5-oxo-heptadeca-12,16-dienoic acid

Analogously to Example 1at, from 284 mg (0.34 mmole) of the compound described under 28v, after purification, 235 mg (81%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.00 (3H), 0.02 (3H), 0.04 (3H), 0.09 (3H), 0.14 (3H9 [typo in German, should be (3H) - T.], 0.19 (3H) [ditto], 0.87-0.96 (30H), 1.13 (3H), 1.70 (3H), 1.95 (3H), 2.12-2.30 (3H), 2.70 (3H), 3.00 (1H), 3.80 (1H), 4.13 (1H), 4.49 (1H), 5.18 (1H), 6.63 (1H), 6.93 (1H) ppm.

Example 28x

(3S,6R,7S,8S,12Z,15S,16E)-3,7-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-15-hydroxy-17-(2-methylthiazol-4-yl)-6,8,12,16-tetramethyl-4,4-trimethylene-5-oxo-heptadeca-12,16-dienoic acid

Analogously to Example 1i, from 230 mg (0.27 mmole) of the compound described under 28w, 200 mg (100%) of the compound in the title are obtained, which is used in the next step without purification.

^{1}H-NMR ($CDCl_3$): δ = 0.05 (3H), 0.10 (6H), 0.19 (3H), 0.90 (18H), 0.95 (3H), 1.12 (3H), 1.70 (3H), 2.00 (3H), 2.70 (3H), 3.00 (1H), 3.84 (1H), 4.15 (1H), 4.49 (1H), 5.15 (1H), 6.67 (1H), 6.91 (1H) ppm.

Example 28y

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-16-(1-methyl-2-(2-methylthiazol-4-yl)ethenyl)-1-oxa-7,9,13-trimethyl-5,5-trimethylene-cyclohexadec-13-ene-2,6-dione

Analogously to Example 1aw, from 200 mg (0.27 mmole) of the compound described under 28x, after purification, 101 mg (52%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = -0.05 (3H), 0.12 (3H), 0.15 (6H), 0.82 (9H), 0.98 (9H), 1.00 (3H), 1.24 (3H), 1.68 (3H), 2.11 (3H), 2.28 (1H), 2.47 (1H), 2.60-2.70 (2H), 2.72 (3H), 2.98 (1H), 3.93 (1H), 4.41 (1H), 5.03 (1H), 5.17 (3H), 6.58 (1H), 6.98 (1H) ppm.

Example 28

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7,9,13-trimethyl-5,5-trimethylene-cyclohexadec-13-ene-2,6-dione

Analogously to Example 1, from 101 mg (0.14 mmole) of the compound described under 28y, 51 mg (73%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.28 (3H), 1.67 (3H), 2.09 (3H), 2.70 (3H), 3.01 (1H), 3.73 (1H), 4.46 (1H), 5.14 (1H), 5.19 (1H), 6.60 (1H), 6.96 (1H) ppm.

Example 29

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10,12,16-trimethyl-8,8-trimethylene-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and

(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10,12,16-trimethyl-8,8-trimethylene-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B)

Analogously to Example 14, from 47 mg (0.09 mmole) of the compound described under 28, 29 mg (59%) of compound A in the title and 7 mg (14%) of compound B in the title are obtained after separation.

^{1}H-NMR ($CDCl_3$) of compound A: δ = 1.01 (3H), 1.24 (3H), 1.28 (3H), 2.09 (3H), 2.72 (3H), 2.78 (1H), 3.05 (1H), 3.72 (1H), 4.20 (1H), 4.45 (1H), 5.37 (1H), 6.59 (1H), 6.96 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of compound B: δ = 0.94 (3H), 1.20 (3H), 1.26 (3H), 2.12 (3H), 2.71 (3H), 2.99 (1H), 3.11 (1H), 4.41 (1H), 4.39 (1H), 5.60 (1H), 6.62 (1H), 6.99 (1H) ppm.

Example 30

(4S,7R,8S,9S,13(E),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7,9,13-trimethyl-5,5-trimethylene-cyclohexadec-13-ene-2,6-dione

Example 30a

(3S,6R,7S,8S,12E,15S,16E)-1,3,7,15-Tetrakis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-6,8,12,16-tetramethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-heptadeca-12,16-dien-5-one

Analogously to Example 1aq, from 227 mg (0.27 mmole) of compound B described under 28s, 230 mg (90%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.01 (3H), 0.03 (3H), 0.04 (3H), 0.06 (3H), 0.08 (3H), 0.11 (3H), 0.15 (3H), 0.17 (3H), 0.87-0.98 (39H), 1.06 (3H), 1.57 (3H), 2.00 (3H), 2.20-2.39 (3H), 2.70 (3H), 3.09 (1H), 3.61 (2H), 3.78 (1H), 4.10 (2H), 5.14 (3H), 6.45 (1H), 6.91 (1H) ppm.

Example 30b

(3S,6R,7S,8S,12E,15S,16E)-3,7,15-tris-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-1-hydroxy-6,8,12,16-tetramethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-heptadeca-12,16-dien-5-one

Analogously to Example 1ar, from 230 mg (0.24 mmole) of the compound described under 30a, 170 mg (84%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.01 (3H), 0.06 (3H), 0.08 (3H), 0.10 (3H), 0.17 (3H), 0.19 (3H), 0.85-1.00 (30H), 1.10 (3H), 1.62 (3H), 2.15-2.40 (3H), 2.71 (3H), 3.12 (1H), 3.63 (2H), 3.79 (1H), 4.09 (2H), 5.13 (1H), 6.42 (1H), 6.90 (1H) ppm.

Example 30c

(3S,6R,7S,8S,12E,15S,16E)-3,7,15-tris-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-6,8,12,16-tetramethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-5-oxo-heptadeca-12,16-dien-1-al

Analogously to Example 1k, from 170 mg (0.20 mmole) of the compound described under 30b, after filtration through silica gel, 170 mg (100%) of the compound in the title are obtained.

Example 30d

(3S,6R,7S,8S,12E,15S,16E)-3,7,15-tris-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4,6,8,12,16-tetramethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-5-oxo-heptadeca-12,16-dienoic acid

Analogously to Example 1at, from 170 mg (0.20 mmole) of the compound described under 30c, after purification, 144 mg (83%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.01 (3H), 0.05 (3H), 0.06 (3H), 0.09 (3H), 0.15 (3H), 0.20 (3H), 0.85-1.00 (30H), 1.12 (3H), 1.55 (3H), 1.97 (3H), 2.71 (3H), 3.09 (1H), 3.82 (1H), 4.10 (1H), 4.41 (1H), 5.11 (1H), 6.46 (1H), 6.95 (1H) ppm.

Example 30e

(3S,6R,7S,8S,12E,15S,16E)-3,7-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-15-hydroxy-17-(2-methylthiazol-4-yl)-6,8,12,16-tetramethyl-4,4-trimethylene-5-oxo-heptadeca-12,16-dienoic acid

Analogously to Example 1i, from 140 mg (0.16 mmole) of the compound described under 30d, 121 mg (100%) of the compound in the title are obtained, which are used in the next step without purification.

^{1}H-NMR ($CDCl_3$): δ = 0.05 (3H), 0.09 (6H), 0.18 (3H), 0.85-0.95 (18H), 0.98 (3H), 1.11 (3H), 1.61 (3H), 2.00 (3H), 2.69 (3H), 3.02 (1H), 3.82 (1H), 4.15 (1H), 4.40 (1H), 5.15 (1H), 6.54 (1H), 6.91 (1H) ppm.

Example 30f

(4S,7R,8S,9S,13(E),16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-16-(1-methyl-2-(2-methylthiazol-4-yl)ethenyl)-1-oxa-7,9,13-trimethyl-5,5-trimethylene-cyclohexadec-13-ene-2,6-dione

Analogously to Example 1aw, from 121 mg (0.16 mmole) of the compound described under 30e, after purification, 55 mg (48%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.01 (3H), 0.09 (3H), 0.15 (6H), 0.92 (9H), 0.96 (9H), 0.98 (3H), 1.26 (3H), 1.50 (3H), 2.19 (3H), 2.73 (3H), 2.91 (1H), 4.18 (1H), 4.63 (1H), 5.09 (1H), 5.31 (1H), 6.53 (1H), 6.93 (1H) ppm.

Example 30

(4S,7R,8S,9S,13(E),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7,9,13-trimethyl-5,5-trimethylene-cyclohexadec-13-ene-2,6-dione

Analogously to Example 1, from 55 mg (0.08 mmole) of the compound described under 30f, 27 mg (67%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 1.03 (3H), 1.23 (3H), 1.55 (3H), 2.07 (3H), 2.72 (3H), 3.04 (1H), 3.32 (1H), 3.51 (1H), 3.70 (1H), 4.46 (1H), 5.06 (1H), 5.49 (1H), 6.59 (1H), 7.02 (1H) ppm.

Example 31

(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10,12,16-trimethyl-8,8-trimethylene-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10,12,16-trimethyl-8,8-trimethylene-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B)

Analogously to Example 14, from 25 mg (0.05 mmole) of the compound described under 30, 10 mg (39%) of compound A in the title and 8 mg (31%) of compound B in the title are obtained after separation.

^{1}H-NMR ($CDCl_3$) of compound A: δ = 1.02 (3H), 1.25 (3H), 1.27 (3H), 2.08 (3H), 2.71 (3H), 2.84 (1H), 3.13 (1H), 3.72 (1H), 4.93 (1H), 5.51 (1H), 6.68 (1H), 7.04 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of compound B: δ = 0.98 (3H), 1.27 (3H), 1.28 (3H), 2.11 (3H), 2.89 (1H), 3.08 (1H), 3.70 (1H), 4.48 (1H), 5.43 (1H), 6.58 (1H), 6.97 (1H) ppm.

Example 32

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-9,13-dimethyl-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-trimethylene-cyclohexadec-13-ene-2,6-dione

Example 32a

1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]-α-propylcyclobutanemethanol

Analogously to Example 11, from 24.15 g (105.8 mmole) of the compound described under 28c, after purification, 20.81 g (72%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.09 (6H), 0.93 (9H), 0.95 (3H), 1.36 (3H), 1.48-1.80 (3H), 1.87 (3H), 2.08 (1H), 3.18 (1H), 3.56 (1H), 3.72 (1H), 3.86 (1H) ppm.

Example 32b

1-[1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]cyclobut-1-yl]-1-butanone

Analogously to Example 1k, from 20.81 g (76.34 mmole) of the compound described under 32a, after filtration through silica gel, 20.7 g (100%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.05 (6H), 0.88 (9H), 0.92 (3H), 1.59 (2H), 1.75-1.95 (4H), 2.23-2.34 (2H), 2.43 (2H), 3.81 (2H) ppm.

Example 32c

1-[1-[Hydroxymethyl)cyclobut-1-yl]-1-butanone

Analogously to Example 1i, from 20.7 g (76.34 mmole) of the compound described under 32b, after purification, 11.57 g (97%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.94 (3H), 1.64 (2H), 1.85-2.10 (4H), 2.29-2.43 (2H), 2.53 (2H), 3.87 (2H) ppm.

Example 32d

1-(1-Oxobutyl)cyclobutanecarbaldehyde

Analogously to Example 1k, from 2.34 g (15 mmole) of the compound described under 32c, after filtration through silica gel, 2.31 g (100%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.92 (3H), 1.62 (2H), 1.85-2.01 (4H), 2.38-2.55 (6H), 9.69 (1H) ppm.

Example 32e

(4*S*,5*R*)-3-(Bromoacetyl)-4-methyl-5-phenyloxazolidin-2-one

To a solution of 33.06 g (186.6 mmole) of (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one in 500 mL of tetrahydrofuran, 82 mL of a 2.5 molar solution of butyllithium in hexane are added over a period of 30 minutes at -70°C under argon. Then, a solution of 15.55 mL (187 mmole) of bromoacetyl chloride in 250 mL of tetrahydrofuran is added dropwise in such a way that the inside temperature does not exceed -65°C. Then, stirring is continued for an hour at -70°C. Then the reaction mixture is poured onto 50 mL of saturated aqueous ammonium chloride solution. Then 90 mL of saturated aqueous sodium hydrogen carbonate solution are added, the temperature is allowed to rise to 25°C, followed by dilution with water and extraction with ethyl acetate. The organic phase is washed with aqueous sodium chloride solution, dried over sodium sulfate and chromatographed over silica gel. Thus, 42.32 g (76%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.95 (3H), 4.57 (2H), 4.80 (1H), 5.76 (1H), 7.2-7.5 (5H) ppm.

Example 32f

[4*S*-[3(*R),4α,5α]]-3-[3-Hydroxy-1-oxo-3-[1-(1-oxobutyl)cyclobut-1-yl]propyl]-4-methyl-5-phenyloxazolidin-2-one**

To a suspension of 5 g (40.68 mmole) of anhydrous chromium(II) chloride in 60 mL of tetrahydrofuran, 200 mg (1.5 mmole) of anhydrous lithium iodide are added under argon. Then, a mixture of 5 g (16.77 mmole) of the compound described under 32e and 2.31 g (15 mmole) of the compound described under 32d in 10 mL of tetrahydrofuran are added (exothermic reaction, the inside temperature should not exceed 35°C). Stirring is continued for one hour at 25°C and then, under gentle cooling, 50 mL of saturated aqueous sodium chloride solution are added. Stirring is continued for another 30 minutes at 25°C. Then the mixture is extracted with ethyl acetate. The organic phase is washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and chromatographed over silica gel. Thus, 3.89 g (69%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.90-0.99 (6H), 1.58-1.73 (4H), 1.79-2.05 (2H), 2.10-2.69 (7H), 3.00-3.12 (2H), 3.44 (1H), 4.39 (1H), 4.78 (1H), 5.70 (1H), 7.27-7.33 (2H), 7.35-7.48 (3H) ppm.

Example 32g

[4*S*-[3(*R),4α,5α]]-3-[3-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-1-oxo-3-[1-(1-oxobutyl)-cyclobut-1-yl]propyl]-4-methyl-5-phenyloxazolidin-2-one**

Analogously to Example 1aq, from 3.89 g (10.42 mmole) of the compound described under Example 32f, after purification, 3.94 g (76%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.08 (3H), 0.20 (3H), 0.85-0.98 (15H), 1.55-1.93 (4H), 2.03 (1H), 2.20-2.38 (3H), 2.45-2.67 (2H), 2.91-3.13 (2H), 4.62-4.75 (2H), 5.67 (1H), 7.29-7.47 (5H) ppm.

Example 32h

(S)-3-[3-[[Dimethyl(1,1-dimethyl)silyl]oxy]-3-[1-(1-oxopropyl)cyclobut-1-yl]propanoicacid

To a solution of 3.94 g (8.08 mmole) of the compound described under 32g in 40 mL of a mixture of tetrahydrofuran and water (4:1), 3.29 mL (32.3 mmole) of a 30% hydrogen peroxide solution are added at 0°C (exothermic reaction, the inside temperature should not rise above 15°C). Stirring is continued for 5 minutes at 0°C and then a solution of 309 mg (32.3 mmole) of lithium hydroxide in 16 mL of water is added. Then stirring is continued for 3 hours at 0°C. Then the reaction mixture is poured carefully into ice-cold sodium thiosulfate solution. Stirring is continued for 5 minutes at 0°C and 15 minutes at 25°C. Then the tetrahydrofuran is removed in vacuum and the remaining solution is acidified to pH = 1 with 5 N hydrochloric acid. It is extracted with dichloromethane. The organic phase is washed with aqueous saturated sodium chloride solution, dried over sodium sulfate and chromatographed over silica gel. Thus, 2.34 g (89%) of the compound in the title and 1.04 g (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one are obtained, which can be used again in Example 32e.

^{1}H-NMR ($CDCl_3$): δ = 0.09 (3H), 0.18 (3H), 0.86-0.97 (12H), 1.59 (2H), 1.56-1.94 (3H), 2.05-2.36 (4H), 2.40-2.57 (3H), 4.44 (1H) ppm.

Example 32i

(3S,6R,7S,8S,12Z,15S,16E)-3,7-15-tris-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-6-ethyl-8,12,16-trimethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-5-oxo-heptadeca-12,16-dienoic acid (A) and

(3S,6R,7S,8S,12E,15S,16E)-3,7,15-tris-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-6-ethyl-8,12,16-trimethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-5-oxo-heptadeca-12,16-dienoic acid (B) and

(3S,6S,7R,8S,12Z,15S,16E)-3,7,15-tris-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-6-ethyl-8,12,16-trimethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-5-oxo-heptadeca-12,16-dienoic acid (C) and

(3S,6S,7R,8S,12E,15S,16E)-3,7,15-tris-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-6-ethyl-8,12,16-trimethyl-4,4-trimethylene-17-(2-methylthiazol-4-yl)-5-oxo-heptadeca-12,16-dienoic acid (D)

Analogously to Example 1ak, starting from 842 µL (5.99 mmole) of diisopropylamine and 3.74 mL (5.99 mmole) of a 1.6 molar solution of butyllithium in hexane in 5 mL of absolute tetrahydrofuran, lithium diisopropylamide is prepared. To this solution, at -78°C, a solution of 787 mg (2.4 mmole) of the compound described under 32h in 5 mL of absolute tetrahydrofuran is added. Stirring is continued for 1 hour at -40°C. Then the mixture is cooled again to -78°C and the solution of 524 mg (1.2 mmole) of the compound described under 28r in 5 mL of absolute tetrahydrofuran is added. Stirring is continued for another hour at -78°C. Then the reaction mixture is poured into saturated aqueous ammonium chloride solution, 0.45 mL of glacial acetic acid is added and the stirring is continued for one hour. Then it is extracted with ethyl acetate. The organic phase is washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. The obtained crude product (maximum 920 mg (100%)) is dissolved in 10 mL of dichloromethane and converted into the persilylated compound analogously to Example 1aq. The crude product thus obtained is dissolved in 30 mL of a 1:1 mixture of dichloromethane and methanol. At 0°C, 280 mg (1.2 mmole) of DL-camphorsulfonic acid are added and stirring is continued for 2.5 hours at this temperature. Then 2.5 mL of triethylamine are added. Then the mixture is evaporated in vacuum. The residue is taken up in dichloromethane. It is washed with 1 normal hydrochloric acid and saturated aqueous sodium chloride solution. It is dried over sodium sulfate and evaporated in vacuum. The obtained crude product is separated by repeated chromatography on a silica gel column. Thus, 229 mg (22%) of compound A, 174

mg (17%) of compound B as well as 292 mg (28%) of a mixture of compounds C and D are obtained.

^{1}H-NMR ($CDCl_3$) of compound A: δ = 0.00 (3H), 0.02 (3H), 0.04 (3H), 0.08 (3H), 0.13 (3H), 0.18 (3H), 0.85-0.99 (33H), 1.79 (3H), 1.94 (3H), 2.10-2.28 (5H), 2.30-2.45 (2H), 2.48 (H), 2.70 (3H), 2.90 (1H), 3.78 (1H), 4.17 (1H), 4.46 (1H), 5.19 (1H), 6.64 (1H), 6.95 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of compound B: δ = 0.00 (3H), 0.03 (3H), 0.06 (3H), 0.07 (3H), 0.14 (3H), 0.19 (3H), 0.78-0.98 (33H), 1.55 (3H), 1.92 (3H), 2.12-2.50 (10H), 2.69 (3H), 2.72 (1H), 3.00 (1H), 3.88 (1H), 4.08 (1H), 4.41 (1H), 5.10 (1H), 6.48 (1H), 6.94 (1H) ppm.

Example 32k

(3S,6R,7S,8S,12Z,15S,16E)-3,7-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-15-hydroxy-17-(2-methylthiazol-4-yl)-6-ethyl-8,12,16-trimethyl-4,4-trimethylene-5-oxo-heptadeca-12,16-dienoic acid

Analogously to Example 1i, from 229 mg (0.26 mmole) of compound A described under 32i, 200 mg (100%) of the compound in the title are obtained, which are used in the next step without purification.

Example 32l

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-16-(1-methyl-2-(2-methylthiazol-4-yl)ethenyl)-1-oxa-7-ethyl-9,13-trimethyl-5,5-trimethylene-cyclohexa-dec-13-ene-2,6-dione

Analogously to Example 1aw, from 200 mg (0.26 mmole) of the compound described under 32k, after purification, 100 mg (51%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.93 (3H), 0.11 (3H), 0.16 (6H), 0.83 (9H), 0.88 (3H), 0.96 (9H), 1.02 (3H), 1.68 (3H), 2.12 (3H), 2.30-2.70 (6H), 2.72 (3H), 3.03 (1H), 4.07 (1H), 4.43 (1H), 5.01 (1H), 5.17 (1H), 6.58 (1H), 6.98 (1H) ppm.

Example 32

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-9,13-dimethyl-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-trimethylene-cyclohexadec-13-ene-2,6-dione

Analogously to Example 1, from 100 mg (0.13 mmole) of the compound described under 32l, after purification, 63 mg (90%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.95 (3H), 1.00 (3H), 1.68 (3H), 2.05 (3H), 2.72 (3H), 2.97 (1H), 3.67 (1H), 4.46 (1H), 5.08 (1H), 5.23 (1H), 6.59 (1H), 6.98 (1H) ppm.

Example 33

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-12,16-dimethyl-10-ethyl-8,8-trimethylene-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and

(1R,3S(E),7S,10R,11S,12R,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-12,16-dimethyl-10-ethyl-8,8-trimethylene-4,17-dioxabicyclo-[14.1.0]heptadecane-5,9-dione (B)

Analogously to Example 14, from 50 mg (0.10 mmole) of the compound described under 32, 24 mg (47%) of compound A in the title and 6 mg (12%) of compound B in the title are obtained.

^{1}H-NMR ($CDCl_3$) of compound A: δ = 0.95 (3H), 0.98 (3H), 1.30 (3H), 2.07 (3H), 2.71 (3H), 2.76 (1H), 3.03 (1H), 3.69 (1H), 4.44 (1H), 5.40 (1H), 6.58 (1H), 6.97 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of compound B: δ = 0.92 (3H), 0.95 (3H), 2.10 (3H), 2.71 (3H), 2.88 (1H), 3.04 (1H), 3.78 (1H), 4.49 (1H), 5.53 (1H), 6.64 (1H), 6.99 (1H) ppm.

Example 34

(4S,7R,8S,9S,13(E),16S(E))-4,8-Dihydroxy-9,13-dimethyl-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-trimethylene-cyclohexadec-13-ene-2,6-dione

Example 34a

(3S,6R,7S,8S,12E,15S,16E)-3,7-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-15-hydroxy-17-(2-methylthiazol-4-yl)-6-ethyl-8,12,16-trimethyl-4,4-trimethylene-5-oxo-heptadeca-12,16-dienoic acid

Analogously to Example 1i, from 174 mg (0.20 mmole) of compound B described in Example 32i, 151 mg (100%) of the compound in the title are obtained, which are used in the next step without further purification.

Example 34b

(4S,7R,8S,9S,13(E),16S(E))-4,8-Bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-16-(1-methyl-2-(2-methylthiazol-4-yl)ethenyl)-1-oxa-7-ethyl-9,13-trimethyl-5,5-trimethylene-cyclohexadec-13-ene-2,6-dione

Analogously to Example 1aw, from 151 mg (0.20 mmole) of the compound described under 34a, after purification, 86 mg (58%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.04 (3H), 0.11 (6H), 0.13 (3H), 0.86 (3H), 0.88 (9H), 0.93 (9H), 1.01 (3H), 1.54 (3H), 2.17 (3H), 2.24-2.46 (3H), 2.72 (3H), 2.83 (1H), 3.03 (1H), 4.08 (1H), 4.53 (1H), 5.13 (1H), 5.27 (1H), 6.53 (1H), 6.96 (1H) ppm.

Example 34

(4S,7R,8S,9S,13(E),16S(E))-4,8-Dihydroxy-9,13-dimethyl-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-trimethylene-cyclohexadec-13-ene-2,6-dione

Analogously to Example 1, from 86 mg (0.12 mmole) of the compound described under 34b, 39 mg (65%) of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 0.93 (3H), 1.06 (3H), 1.53 (3H), 2.03 (3H), 2.69 (3H), 3.09 (1H), 3.82 (1H), 4.52 (1H), 5.03 (1H), 5.36 (1H), 6.60 (1H), 7.03 (1H) ppm.

Example 35

(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-12,16-dimethyl-10-ethyl-8,8-trimethylene-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (A) and

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-12,16-dimethyl-10-ethyl-8,8-trimethylene-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (B)

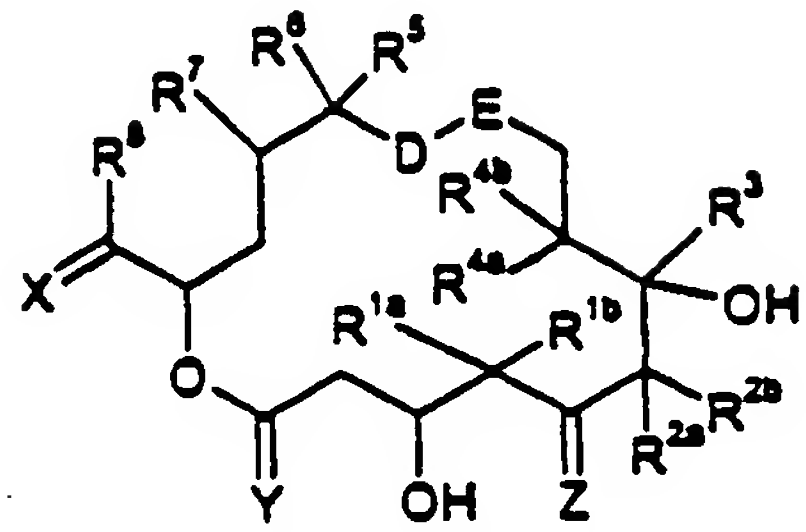
Analogously to Example 14, from 30 mg (0.06 mmole) of the compound described under Example 34, 10 mg (32%) of compound A in the title and 8 mg (26%) of compound B in the title are obtained.

^{1}H-NMR ($CDCl_3$) of compound A: δ = 0.95 (3H), 1.03 (3H), 1.23 (3H), 2.08 (3H), 2.71 (3H), 2.84 (1H), 3.16 (1H), 3.82 (1H), 4.52 (1H), 5.50 (1H), 6.72 (1H), 7.06 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of compound B: δ = 0.93 (3H), 0.98 (3H), 1.22 (3H), 2.06 (3H), 2.70 (3H), 2.88 (1H), 3.05 (1H), 3.62 (1H), 4.46 (1H), 5.41 (1H), 6.60 (1H), 6.96 (1H) ppm.

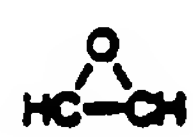
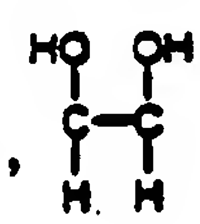
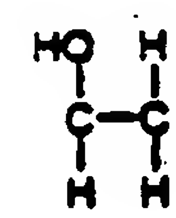
Patent Claims

1. Epothilone derivatives having general formula I,



I,

where

R^{1a}, R^{1b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together for a -$(CH_2)_m$ group with m = 2, 3, 4 or 5,
R^{2a}, R^{2b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together for a -$(CH_2)_n$ group with n = 2, 3, 4 or 5, where, in case
-D-E-	stand for -CH_2-CH_2- or
Y	stands for an oxygen atom,
R^{2a}/R^{2b}	cannot be hydrogen/methyl,
R^3	stands for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,
R^{4a}, R^{4b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl or together for a -$(CH_2)_p$ group with p = 2, 3, 4 or 5,
D-E	stand for a group H_2C-CH_2, $HC=CH$, $C\equiv C$, , , ,
R^5	stands for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,
R^6, R^7	each stand for a hydrogen atom, together for an additional bond or an oxygen atom,
R^8	stands for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20}-aralkyl, all of which may be substituted,
X	stands for a hydrogen atom, two alkoxy groups OR^{23}, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR^9 or a group $CR^{10}R^{11}$, where

R^{23}	stands for a C_1-C_{20} alkyl group,
R^9	stands for hydrogen or a protective group PG^x,
R^{10}, R^{11}	are the same or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl group or
R^{10} and R^{11}	together with the methylene carbon atom stand for a 5- to 7-membered carbocyclic ring,

Y stands for an oxygen atom or two hydrogen atoms,

Z stands for an oxygen atom or H/OR^{12},

where

R^{12} stands for hydrogen or a protective group PG^z.

2. Epothilone derivatives having general formula I according to Claim 1, where Y, Z, R^{1a}, R^{1b}, R^{2a} and R^{2b} all can have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B.

3. Epothilone derivatives having general formula I according to Claim 1, where R^3, R^{4a}, R^{4b}, D-E, R^5, R^6 and R^7 can all have the meanings given in general formula I, and the rest of the molecule is identical with the naturally occurring epothilone A or B.

4. Epothilone derivatives having general formula I according to Claim 1, where R^6, R^7, R^8 and X can all have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B.

5. Epothilone derivatives having general formula I according to Claim 1, where Y, Z, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, D-E, R^5, R^6 and R^7 all can have the meanings given in general formula I, and the rest of the molecule is identical with the naturally occurring epothilone A or B.

6. Epothilone derivatives according to general formula I according to Claim 1, where Y, Z, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^6, R^7, R^8 and X can all have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B.

7. Epothilone derivatives having general formula I according to Claim 1, where R^3, R^{4a}, R^{4b}, D-E, R^5, R^6, R^7, R^8 and X can all have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B.

8. Compounds having general formula I, namely

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione and
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione (B)

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7S,8R,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione and
(4S,7S,8R,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10S,11R,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and
(1R,3S(E),7S,10S,11R,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1S,3S(E),7S,10S,11R,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and (1R,3S(E),7S,10S,11R,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione and (4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((3-pyridyl)-ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and (1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((3-pyridyl)-ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione and (4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-((-4-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((4-pyridyl)-ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and (1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((4-pyridyl)-ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7-phenyl-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-phenyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-phenyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z), 16S(E))-7-Benzyl-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-10-Benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-10-Benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,13-tetramethyl-9-trifluoromethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,16-tetramethyl-12-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,16-tetramethyl-12-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,11E/Z,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-11,13-diene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,14E/Z,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,14E/Z,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-11-ine-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ine-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7.11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ine-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5.7,9-tetramethyl-13-trifluoromethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,12-tetramethyl-16-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,12-tetramethyl-16-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-13-pentafluoroethyl-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-16-pentafluoroethyl-8,8,10,12-tetramethyl-4-17-dioxabicyclo[14.1.0]heptadeca-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-16-pentafluoroethyl-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylene-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8-(1,3-trimethylene)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8-(1,3-trimethylene)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione

(4S,7R,8S,9S,11E/Z,13(E or Z),16S(E))-4,8-Dihydroxy-13-ethyl-16-(1-methyl-2-(2-methyl-4-triazolyl)ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadeca-11,13-diene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,14E/Z,16R)-7,11-Dihydroxy-16-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-14-ene-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,14E/Z,16S)-7,11-Dihydroxy-16-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(4S,7R,8S,9S,11E/Z,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-13-propyl-5,5,7,9-tetramethyl-cyclohexadec-11,13-diene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,14E/Z,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-propyl-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,14E/Z,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-propyl-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(4-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(4-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

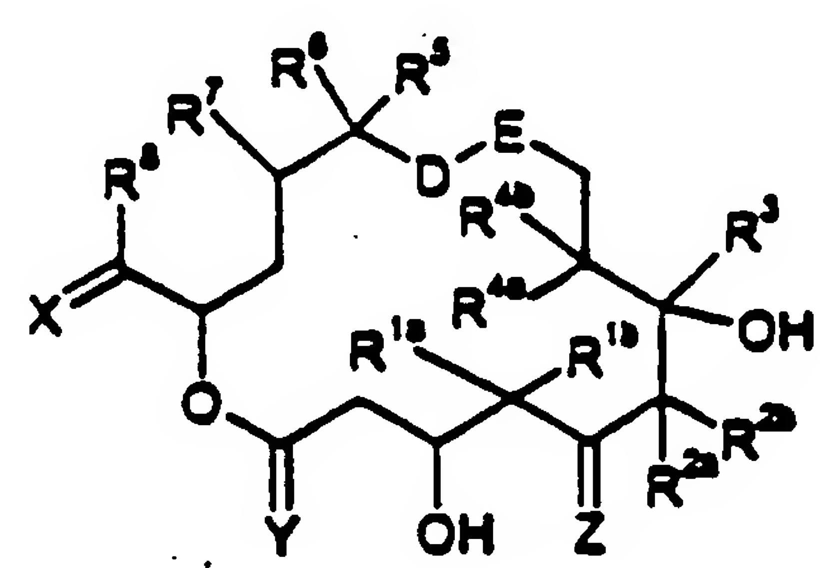
(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(4-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,913[sic]-pentamethyl-cyclohexadec-13-ene-6-one

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-9-one

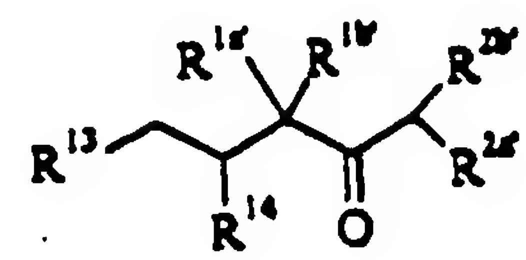
(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-9-one.

9. Method for the preparation of the epothilone derivatives according to general formula I according to Claim 1



I,

where
the substituents have the meanings given in general formula I,
characterized by the fact that
a fragment of general formula A is reacted



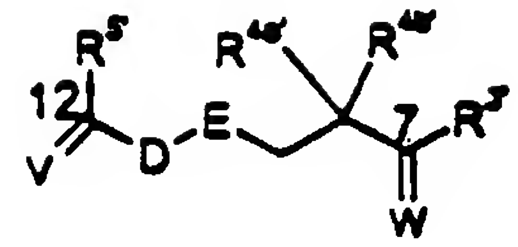
A,

where

$R^{1a'}$, $R^{1b'}$, $R^{2a'}$ and $R^{2b'}$ have the meanings already given for R^{1a}, R^{1b}, R^{2a} and R^{2b} and

R^{13}	stands for CH_2OR^{13a}, CH_2-Hal, CHO, CO_2R^{13b}, COHal,
R^{14}	stands for hydrogen, OR^{14a}, Hal, OSO_2R^{14b},
R^{13a}, R^{14a}	stand for hydrogen, SO_2 alkyl, SO_2 aryl, SO_2 aralkyl or together for a $-(CH_2)_o$ group or together for a $CR^{15a}R^{15b}$ group,
R^{13b}, R^{14b}	stand for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl,
R^{15a}, R^{15b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together for a $-(CH_2)_q$ group,
Hal	is halogen,
o	is 2 to 4,
q	is 3 to 6,

including all stereoisomers as well as their mixtures
as well as
free hydroxyl groups R^{13} and R^{14} can be etherified or esterified in , the free carbonyl groups in A and R^{13} can be ketalized, converted into an enol ether or reduced, as well as the free acid groups in A can be converted into their salts with bases,
with a fragment having formula B



B

where

$R^{3'}$, $R^{4a'}$, $R^{4b'}$ and $R^{5'}$ have the meanings already given for R^3, R^{4a}, R^{4b} and R^5 and

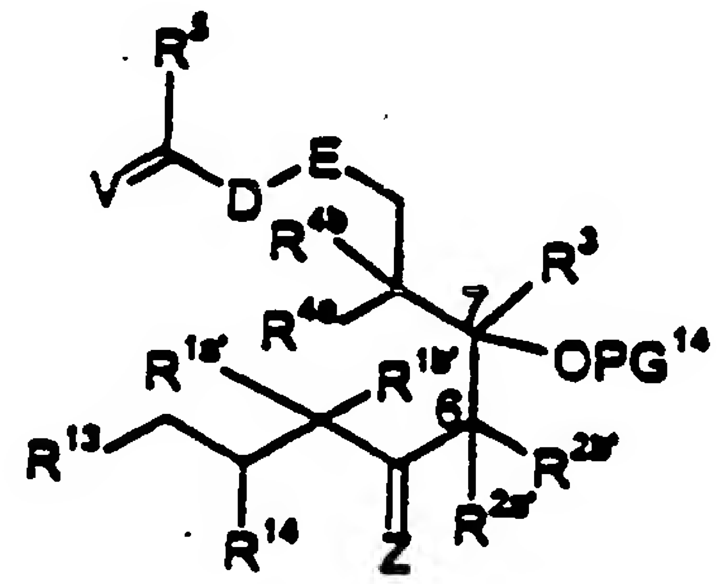
V stands for an oxygen atom, two alkoxy groups OR^{17}, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, or for H/OR^{16},

W stands for an oxygen atom, two alkoxy groups OR^{19}, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched or H/OR^{18},

R^{16}, R^{18} independently of one another, stand for hydrogen or a protective group PG^1,

R^{17}, R^{19} independently of one another, stand for C_1-C_{20} alkyl,

to a partial fragment having general formula AB



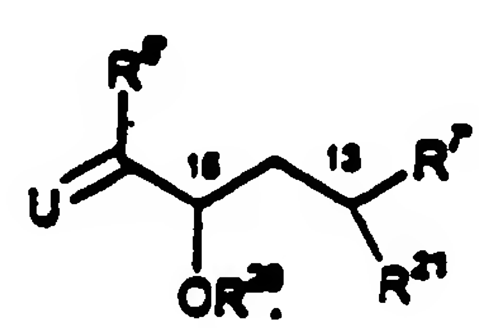
AB,

where

$R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, R^3, R^{4a}, R^{4b}, R^5, R^{13}, R^{14}, D, E, V and Z have the meanings already given and

PG^{14} stands for a hydrogen atom or a protective group PG,

and this partial fragment AB is reacted with a fragment having general formula C



C

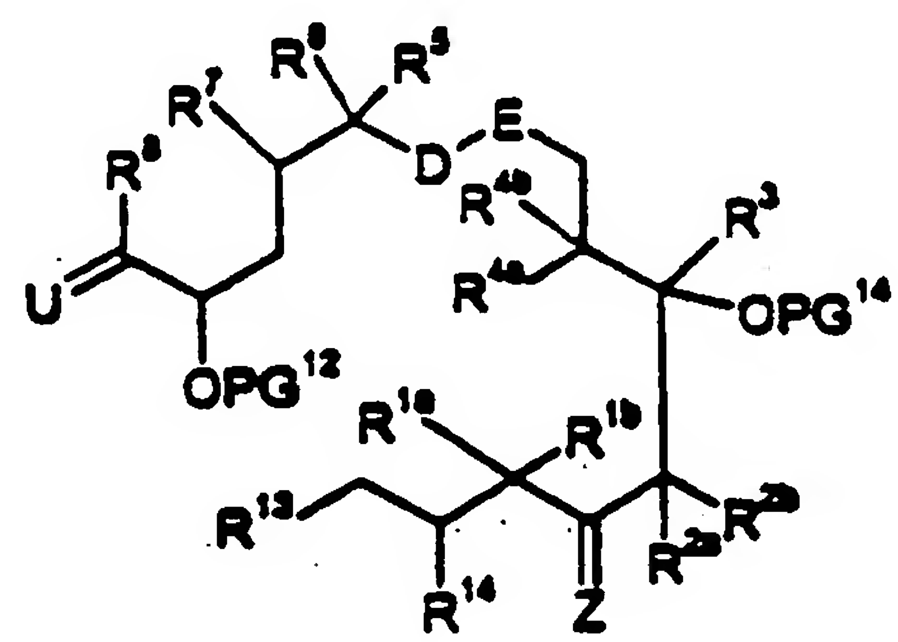
where

$R^{8'}$	has the meaning already given in general formula I for R^8 and
$R^{7'}$	is a hydrogen atom,
R^{20}	is a hydrogen atom or a protective group PG^2,
R^{21}	is a hydroxyl group, halogen, a protected hydroxyl group OPG^3, a phosphonium halide group $PPh_3{}^+Hal^-$ (Ph = phenyl); Hal = F, Cl, Br, I), a phosphonate group $P(O)(OQ)_2$ (Q = C_1-C_{10} alkyl or phenyl) or a phosphine oxide group $P(O)Ph_2$ (Ph = phenyl),
U	stands for an oxygen atom, two alkoxy groups OR^{23}, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR^9 or a group $CR^{10}R^{11}$,

where

R^{23}	stands for a C_1-C_{20} alkyl group,
R^9	stands for hydrogen or a protective group PG^3,
R^{10}, R^{11}	are the same or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl group or
R^{10}, R^{11}	together with the methylene carbon atom stand for a 5- to 7-membered carbocyclic ring,

to a partial fragment having general formula ABC



ABC,

where

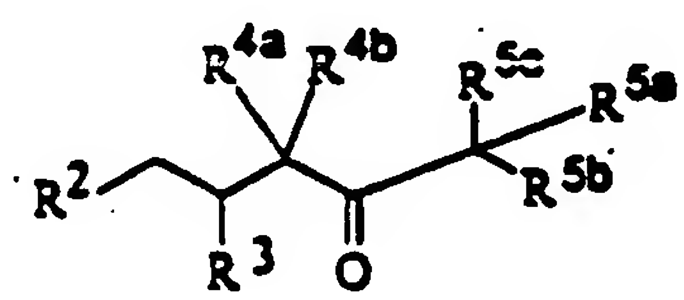
$R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, R^3, R^{4a}, R^{4b}, R^5, R^6, R^7, R^8, R^{13}, R^{14}, D, E, U and Z have the meanings already given above,

and this partial fragment having general formula ABC is cyclized to an epothilone derivative having general formula I.

10. Pharmaceutical preparations containing at least one compound having general formula I according to Claim 1, as well as a pharmaceutically compatible carrier.

11. Application of the compounds according to general formula I according to Claim 1, for the production of drugs.

12. Method for the preparation of compounds having general formula A



A,

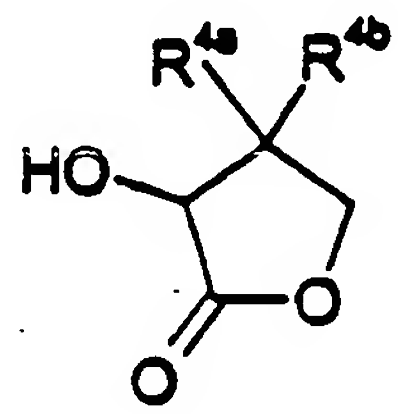
where

R^2	stands for CH_2OR^{2a}, CHO, CO_2R^{2b}, COX,
R^{2a}, R^{2b}	stand for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl,
R^3	stands for hydrogen, OR^{3a}, X, OSO_2R^{3b},
R^{3a}	stands for hydrogen or together with R^{2a} for a $-(CH_2)_n$ group or a $CR^{6a}R^{6b}$ group,
R^{3b}	stands for C_1-C_4-alkyl, aryl,
X	stands for halogen,
n	is 2 to 4,
R^{6a}, R^{6b}	are the same or different and stand for C_1-C_8 alkyl, C_6-C_{10} aryl, or together for a $-(CH_2)_o$ group,
o	is 3 to 6,
R^{6a}	can additionally assume the meaning of hydrogen,
R^{4a}, R^{4b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a $-(CH_2)_m$ group,
m	is 2 to 5,
R^{5a}, R^{5b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl or, together for a $-(CH_2)_p$ group,
p	is 2 to 5,
R^{5c}	is hydrogen,

including all stereoisomers as well as their mixtures

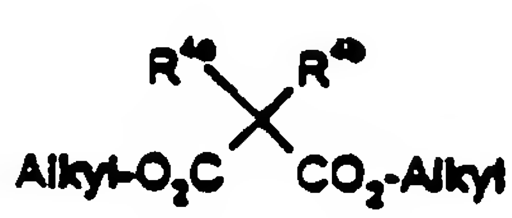
as well as

the free hydroxyl groups in R^2 and R^3 can be etherified or esterified, the free carbonyl groups in A and R^2 can be ketalized, converted into an enol ether or reduced, as well as the free acid groups in A can be converted into their salts with bases,
characterized by the fact that
a) a pantolactone having general formula IIa is used as starting material



II a

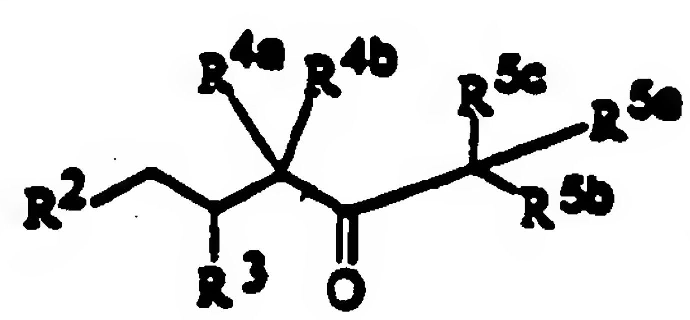
where
R^{4a} and R^{4b} each represent a methyl group
or
b) is a malonic acid dialkyl ester having general formula XXVIII



XXVIII

where
R^{4a}, R^{4b} have the meaning given in general formula A and
alkyl [sic], independently of one another stand for a C_1-C_{20} alkyl, C_3-C_{10} cycloalkyl- or C_4-C_{20} alkylcycloalkyl group.

13. Compounds having general formula A'



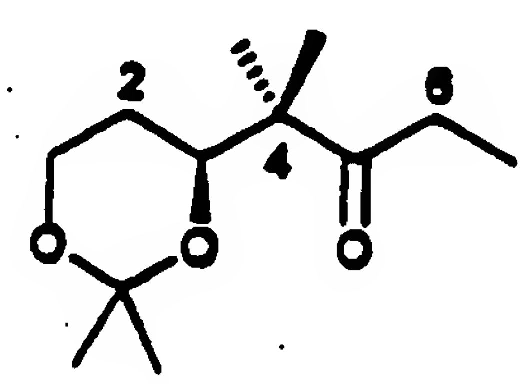
A'

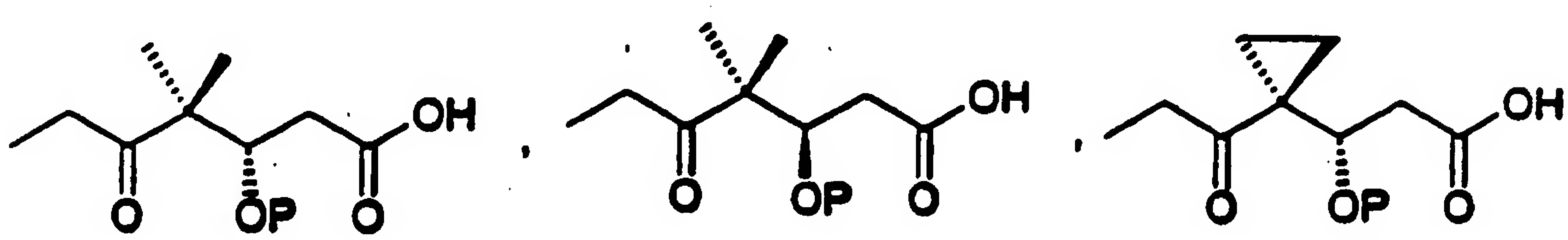
where

R^2	stands for CH_2OR^{2a}, CHO, CO_2R^{2b}, COX,
R^{2a}, R^{2b}	stand for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl,
R^3	stands for hydrogen, OR^{3a}, X, OSO_2R^{3b},
R^{3a}	stands for hydrogen or together with R^{2a} for a -$(CH_2)_n$ group or a $CR^{6a}R^{6b}$ group,
R^{3b}	stands for C_1-C_4 alkyl, aryl,
X	is halogen,
n	is 2 to 4,
R^{6a}, R^{6b}	can be the same or different and can be a C_1-C_8 alkyl, C_6-C_{10} aryl or together can stand for a -$(CH_2)_o$ group,
o	is 3 to 6,
R^{6a}	can additionally assume the meaning of hydrogen,
R^{4a}, R^{4b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a -$(CH_2)_m$ group,
m	is 2 to 5,
R^{5a}, R^{5b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a -$(CH_2)_p$ group,
p	is 2 to 5,
R^{5c}	is hydrogen,

including all stereoisomers as well as their mixtures, as well as the free hydroxyl groups in R^2 and R^3 can be etherified or esterified, the free carbonyl groups in A and R^2 can be ketalized, converted into an enol ether or reduced, as well as the free acid groups in A or can be converted to their salts with bases,

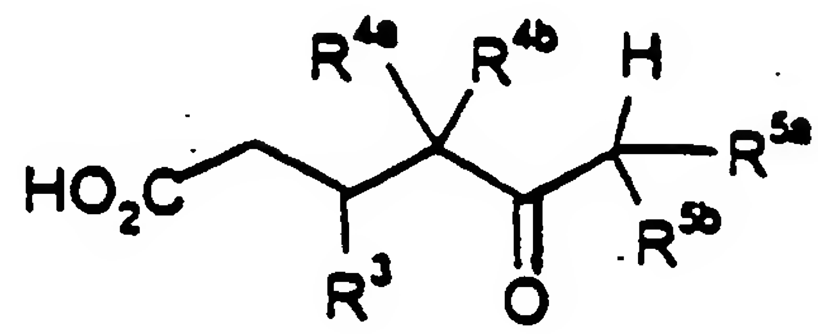
with the exception of the compounds





P = TBS

14. Method for the preparation of compounds having general formula A"



A"

where

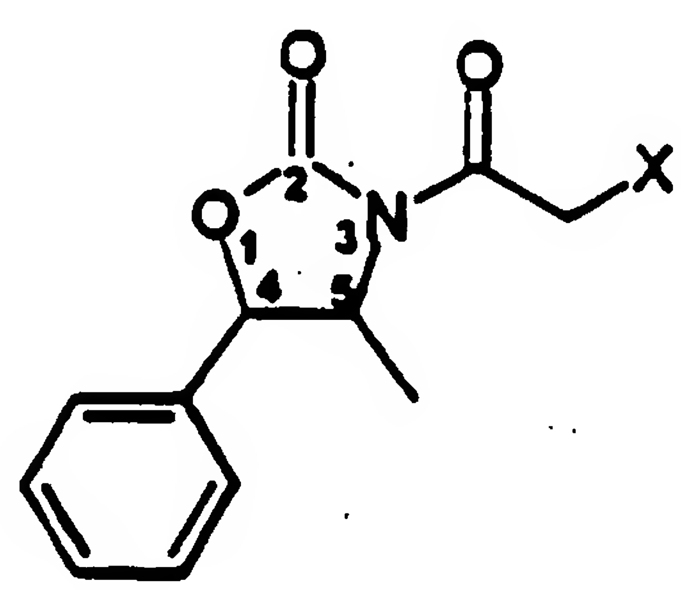
R^3	stands for OR^{3a} and
R^{3a}	stands for hydrogen or a protective group PG
R^{4a}, R^{4B}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a -$(CH_2)_m$ group,
m	is 2 to 5,
R^{5a}, R^{5b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a -$(CH_2)_p$ group,
p	is 2 to 5,

including all stereoisomers as well as their mixtures

as well as

the free carbonyl groups in A" can be ketalized,

characterized by the fact that a compound having general formula II

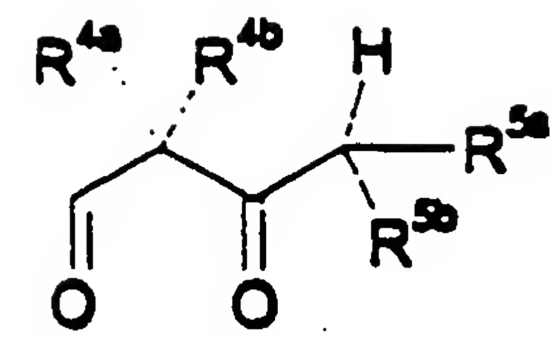


II

where

X is a chlorine or bromine atom, and the 2-oxazolidinone ring has either the (4R,5S)- or the (4S,5R) conformation,

is reacted with a compound having general formula III

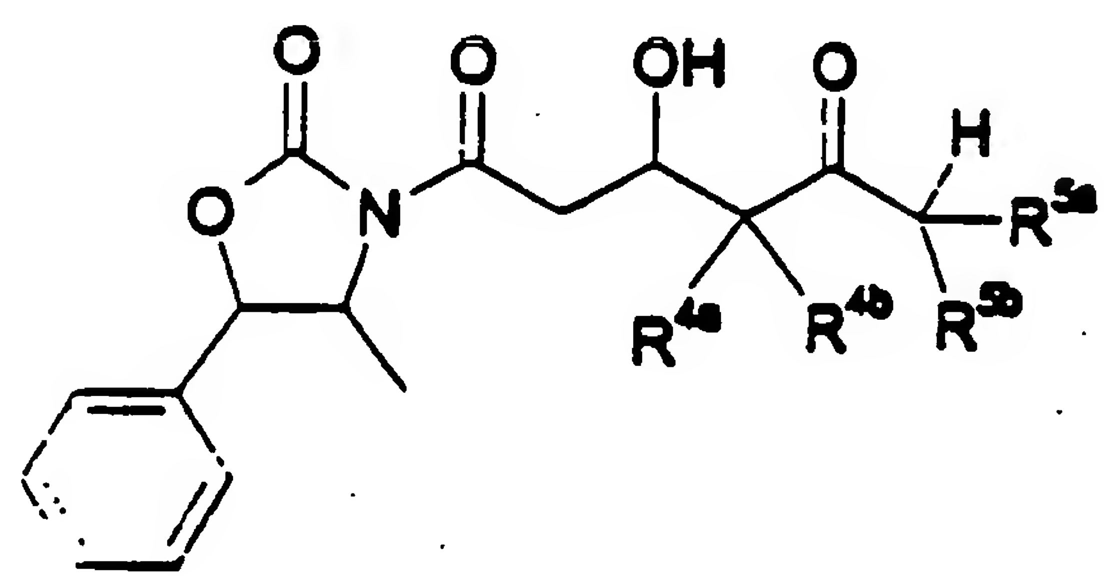


III

where

R^{4a}, R^{4b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a -$(CH_2)_m$ group,
m	is 2 to 5,
R^{5a}, R^{5b}	are the same or different and stand for hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl, or together for a -$(CH_2)_p$ group,
p	is 2 to 5,

to a compound having general formula IV



IV

where

the 2-oxazolidinone ring has the (4R,5S) conformation and the 3' carbon atom has the R conformation or

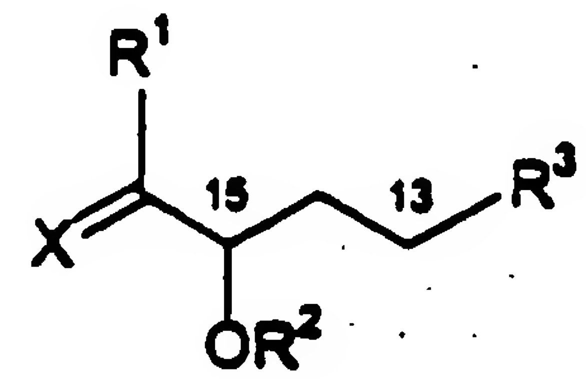
the 2-oxazolidinone ring has the (4S,5R) conformation and the 3' carbon atom has the S conformation,

the 3' hydroxyl group in IV is protected with a protective group PG, the oxazolidinone ring is cleaved off and optionally the protective group PG is cleaved off.

15. Method according to Claim 14, characterized by the fact that the compound having general formula II is reacted in the presence of chromium(II) chloride with a compound having general formula III.

16. Method according to Claim 14 or 15, characterized by the fact that the cleaved-off oxazolidinone ring is recovered in the enantiomerically pure form.

17. Compounds having general formula C,



C,

where

R^1 stands for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl, where all can be substituted,

R^2 stands for hydrogen or a protective group PG^1,

R^3 stands for a hydroxyl group, halogen, a protected hydroxyl group OPG^2, a phosphonium halide group $PPh_3^+Hal^-$ (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate group $P(O)(OQ)_2$ (Q = C_1-C_{10} alkyl or phenyl) or a phosphine oxide group $P(O)Ph_2$ (Ph = phenyl),

X stands for an oxygen atom, two alkoxy groups OR^4, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR^5 or a CR^6R^7 group,

where

R^4 stands for a C_1-C_{20} alkyl group,

R^5 stands for hydrogen or a protective group PG^3,

R^6, R^7 are the same or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl group or R^6 and R^7 together with the methylene carbon atom stand for a 5- to 7-membered carbocyclic ring,

where one cannot have the following at the same time:

R^1 a methyl group, R^2 a tert.-butyldimethylsilyl group or benzyl group, R^3 an O-tert.-butyldimethylsilyl group and X a (2-methylthiazol-4-yl)methylene group or

R^1, a methyl group, R^2 a tert.-butyldimethylsilyl group, R^3 a triphenylphosphonium iodide group and X an (2-methylthiazol-4-yl)methylene group.

18. Compounds according to general formula C according to Claim 17, characterized by the fact that R^1 stands for a hydrogen atom, an optionally substituted C_1-C_4 alkyl group, a phenyl group optionally substituted with 1 to 3 groups, selected from the group of substituents of halogen, free hydroxyl group or protected hydroxyl group OPG^4, C_1-C_4 alkyl, azido, nitro, nitrile, amino (NH_2).

19. Compounds having general formula C according to Claim 17, characterized by the fact that X stands for an oxygen atom.

20. Compounds having general formula C according to Claim 17, characterized by the fact that the aryl group that stands for R^6 and/or R^7 is a phenyl group optionally substituted with 1 to 3 groups selected from the group of substituents of halogen, free hydroxyl group or protected hydroxyl group OPG^5, C_1-C_4 alkyl, azido, nitro, nitrile, amino (NH_2), or for a 5- or 6-membered heteroaryl group, optionally substituted with 1 to 2 C_1 to C_4 alkyl groups.

21. Compounds having general formula C according to Claim 20, characterized by the fact that the aryl group which stands for R^6 and/or R^7 is selected from the group of 2-, 3-furanyl, 2-, 3-, 4-pyridinyl-, 2-, 4-, 5-thiazolyl, 2-, 4- and 5-imidazolyl group, which is optionally substituted by 1 or 2 C_1-C_4 alkyl groups.

22. Compounds having general formula C according to Claim 17, characterized by the fact that the protective groups PG^1, PG^2 and PG^3 are selected from the group of substituents of methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert.-butyldimethylsilyl, tert.-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, para-methoxybenzyl, formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl- or benzoyl group.

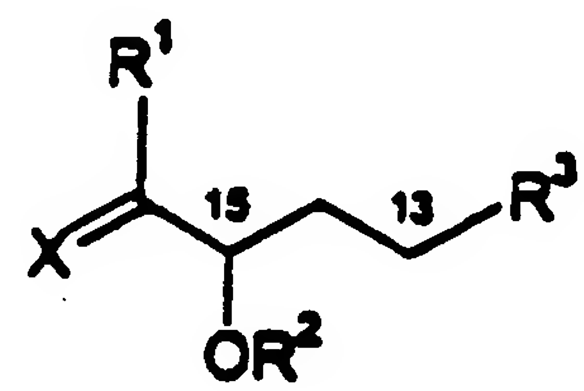
23. Compounds according to Claim 18, characterized by the fact that the protective group PG^4 is selected from the group of substituents of methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert.-butyldimethylsilyl, tert.-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, para-methoxybenzyl, formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl or benzoyl.

24. Compounds according to Claim 20, characterized by the fact that the protective group PG^5 is selected from the group of substituents methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert.-butyldimethylsilyl, tert.-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, para-methoxybenzyl, formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl or benzoyl.

25. Compounds according to Claim 22, characterized by the fact that the protective group PG^1 is a tert.-butyldiphenylsilyl, tert.-butyldimethylsilyl or triisopropylsilyl group.

26. Compounds according to Claim 22, characterized by the fact that the protective group PG^2 is a tert.-butyldimethylsilyl, acetyl, benzoyl, benzyl or tetrahydropyranyl group.

27. Method for the preparation of the compounds having general formula C'



C',

where

R^1 stands for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl, all of which may be substituted,

R^2 stands for hydrogen or a protective group PG^1,

R^2 stands for a hydroxyl group, halogen, a protected hydroxyl group OPG^2, a phosphonium halide group $PPh_3{}^+Hal^-$ (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate group $(P(O)(OQ)_2$ (Q = C_1-C_{10} alkyl or phenyl) or a phosphine oxide group $(P(O)Ph_2$ (Ph = phenyl),

X stands for an oxygen atom, two alkoxy groups OR^4, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR^5 or a CR^6R^7 group,

where

R^4 stands for a C_1-C_{20} alkyl group,

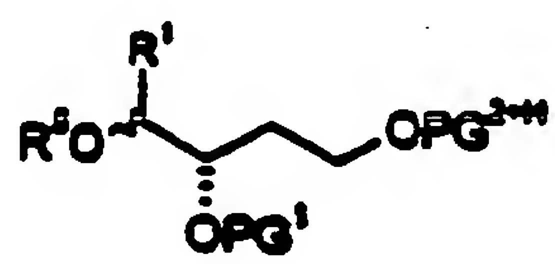
R^5 stands for hydrogen or a protective group PG^3,

R^6, R^7 are the same or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl group or R^6 and R^7 together with the methylene carbon atom stand for a 5- to 7-membered carbocyclic ring,

characterized by the fact that L-(-)-malic acid, D-(+)-malic acid or racemic malic acid is used as starting material.

28. Method according to Claim 27, characterized by the fact that L-(-)-malic acid or D-(+)-malic acid is used.

29. Intermediate compounds having general formula VI"



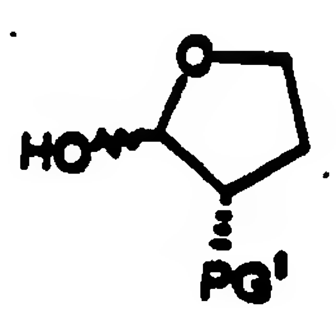
VI"

where

R^1, PG^1 and R^5 have the meaning given in general formula C and

PG^{2+H} stands for a hydrogen atom or a protective group PG^2.

30. Method for the preparation of compounds having the general formula VI" according to Claim 29, characterized by the fact that to a compound having general formula IV



IV

where

PG^1 has the meaning given in general formula C,

an organometallic compound having the following general formula is added with opening of the lactol ring

$$R^1Y$$

where R^1 has the meaning given in general formula C' and
Y stands for an alkali metal atom or MZ, where M is a divalent metal atom and Z is a halogen atom,

and then, optionally,
the primary hydroxyl group is protected with a protective group PG^2 and optionally the secondary hydroxyl group is protected with a protective group PG^3.